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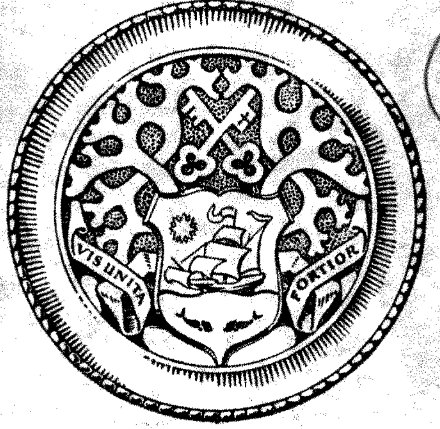

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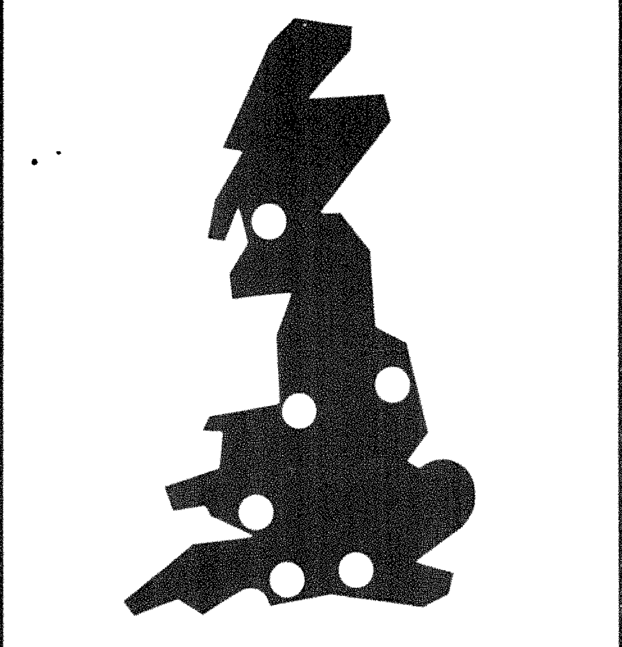

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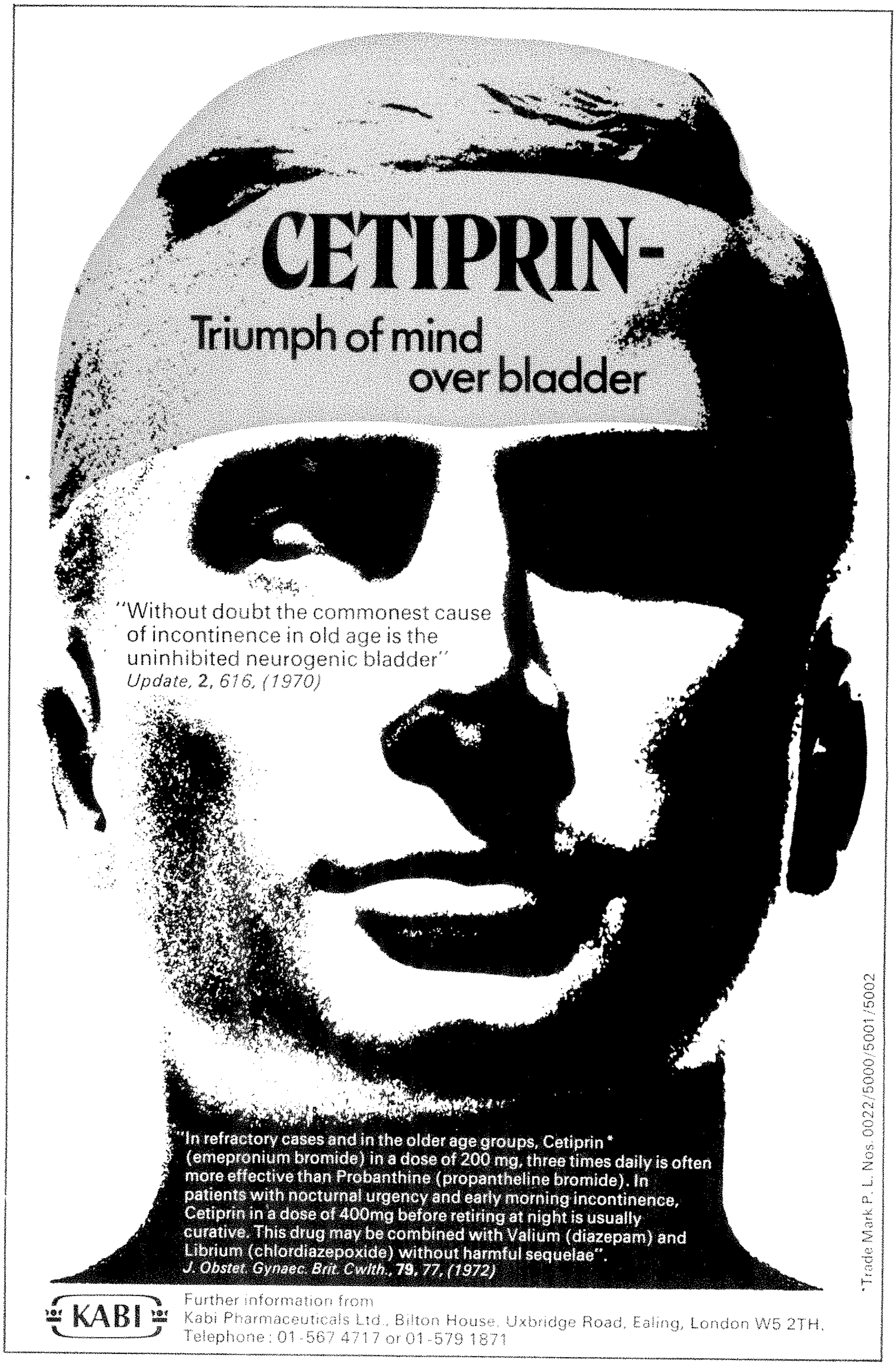

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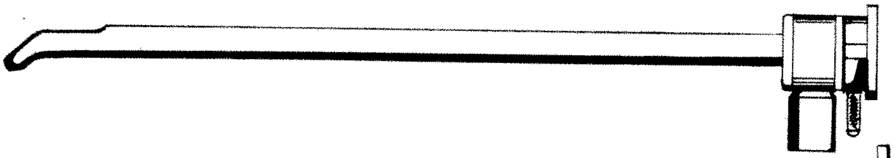

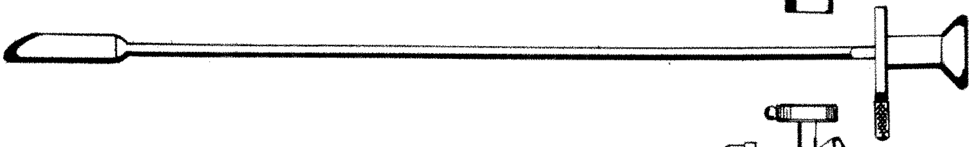

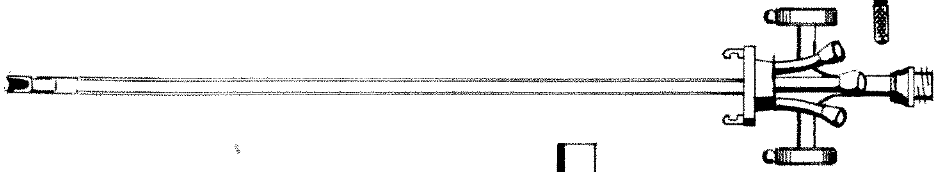

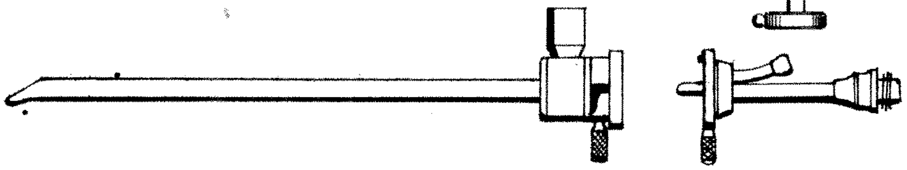

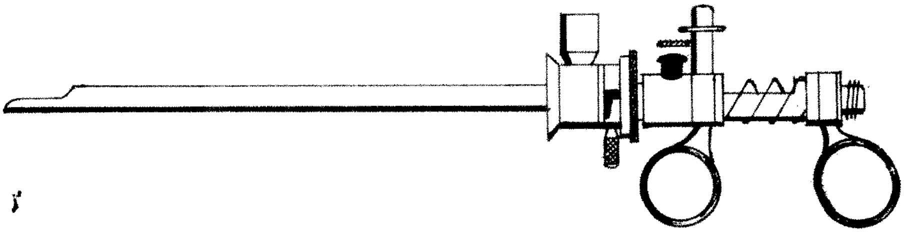

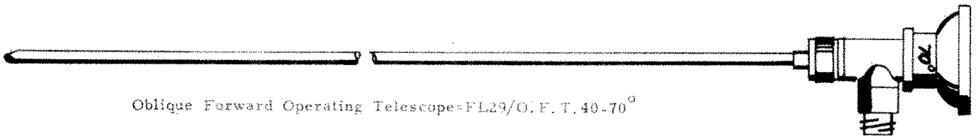

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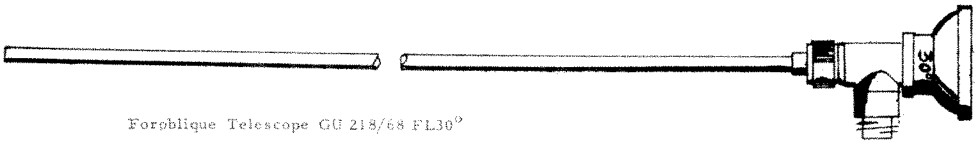

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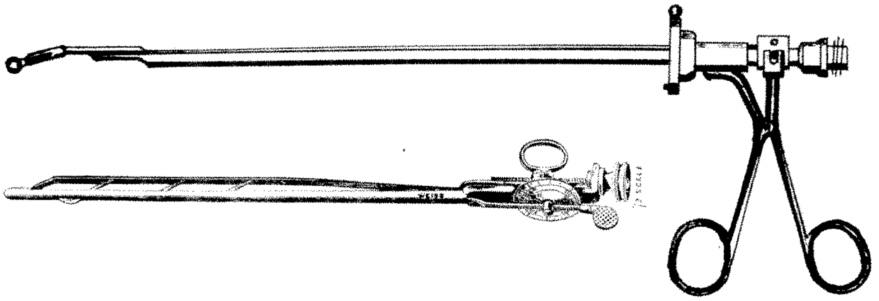

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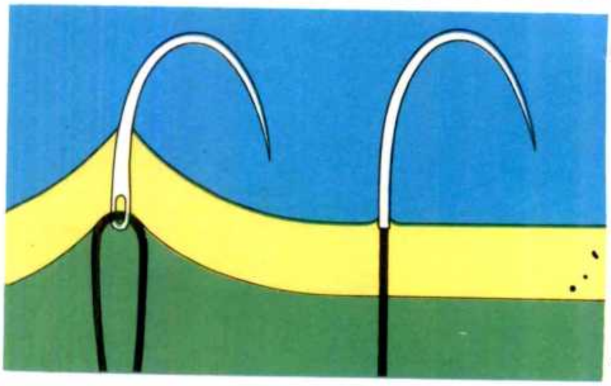

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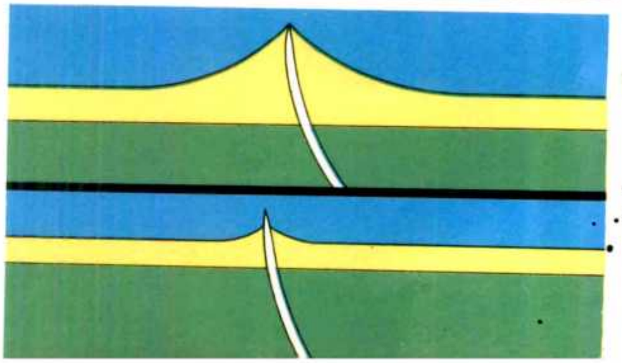

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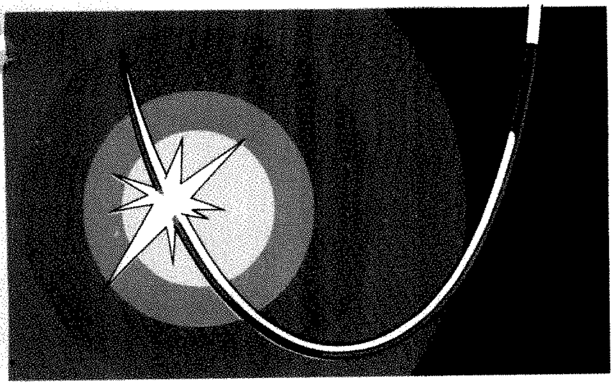

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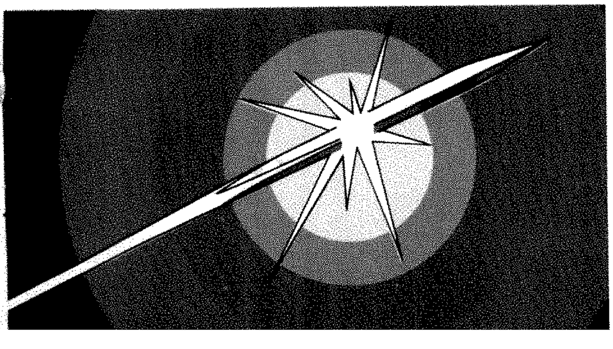

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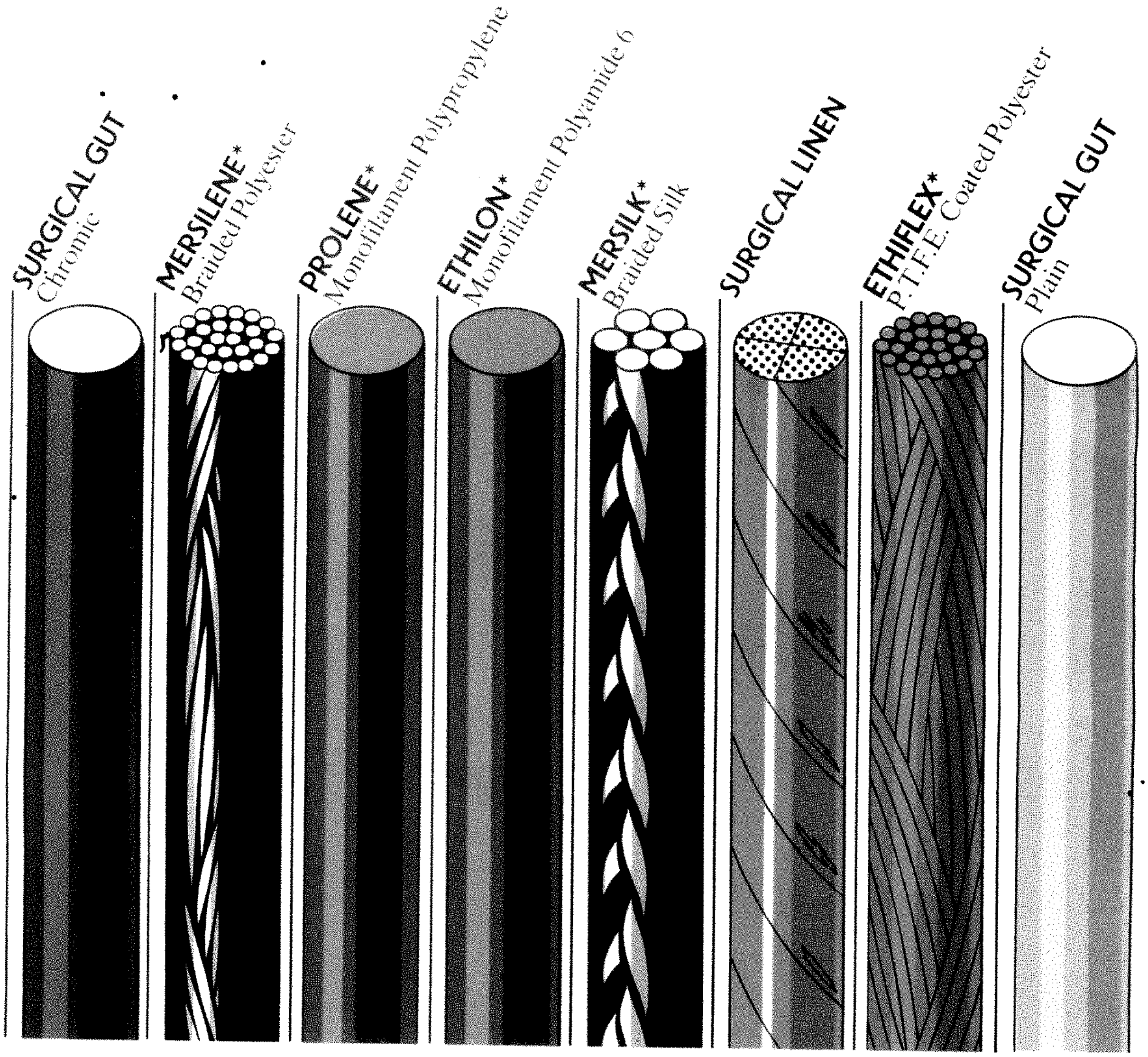

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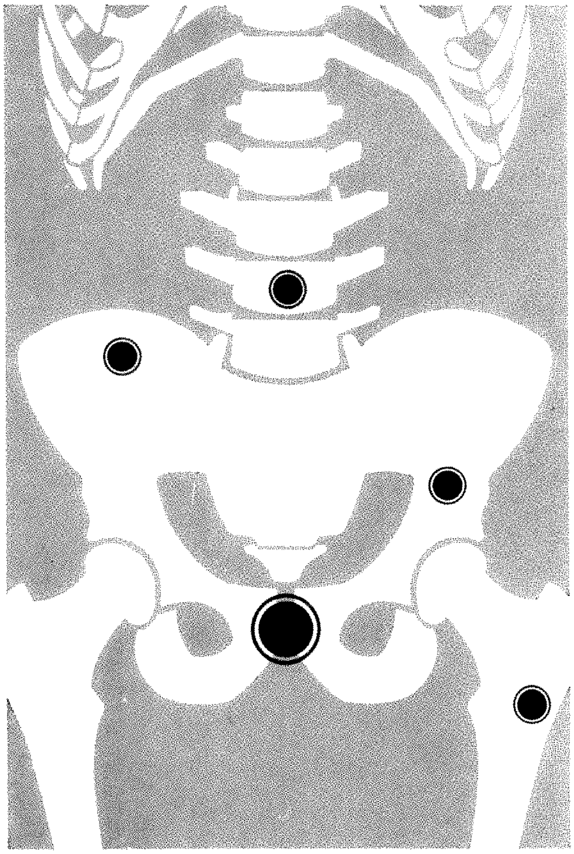

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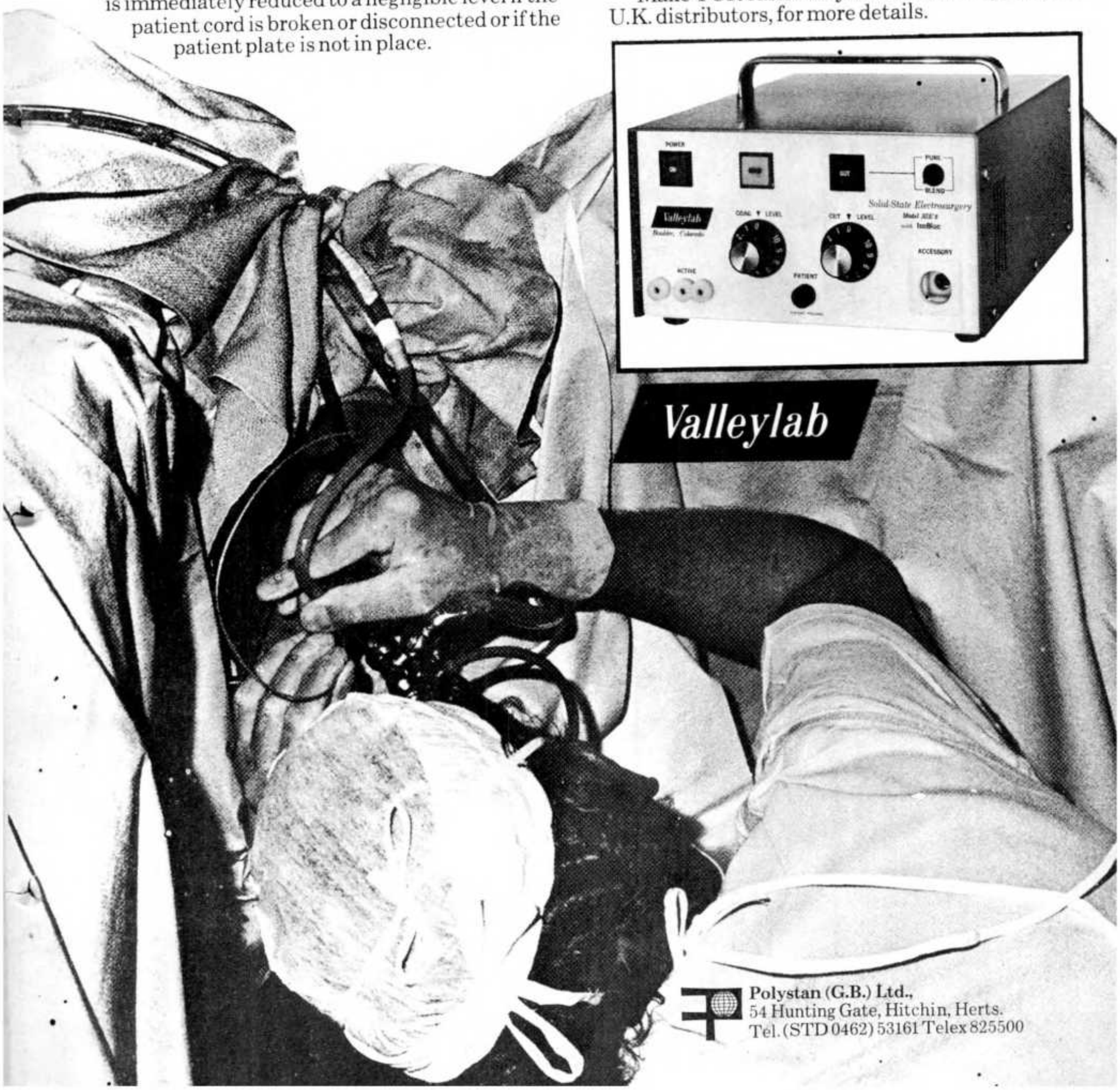

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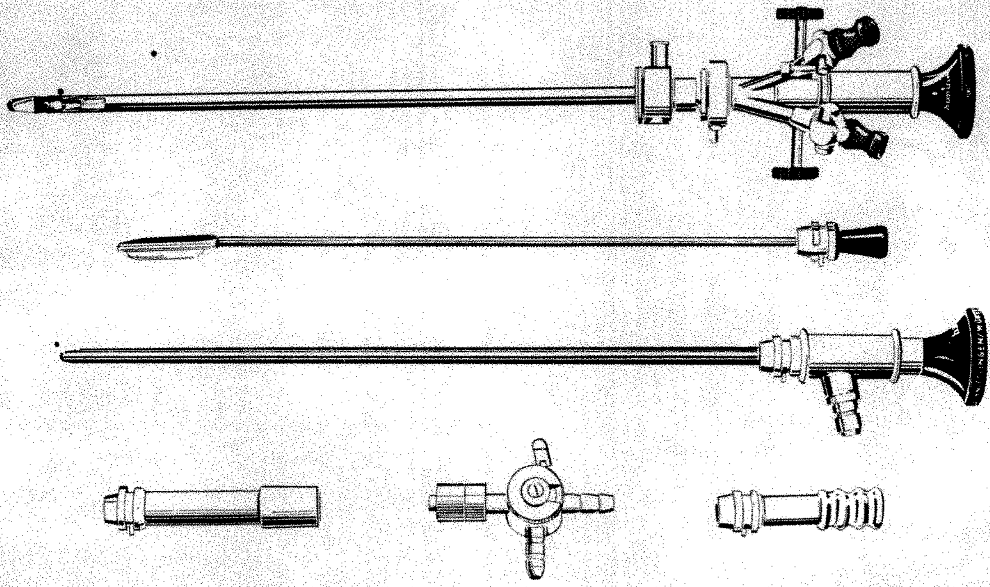

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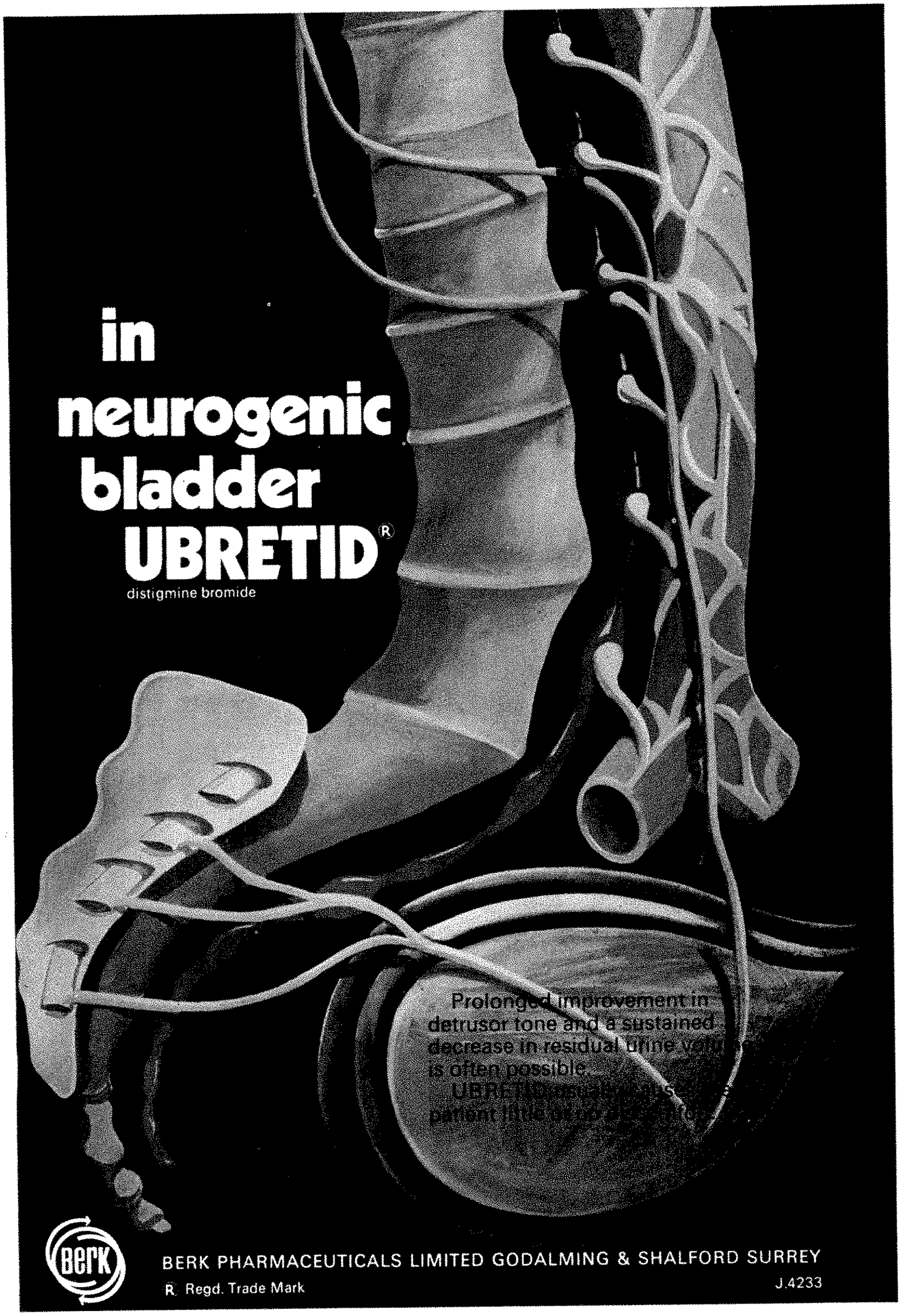

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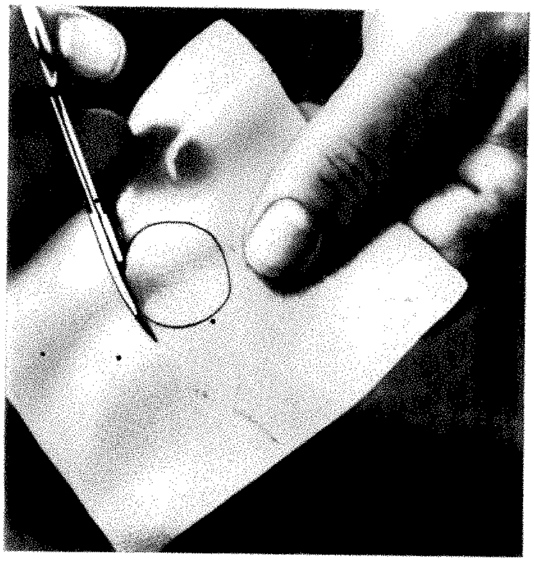

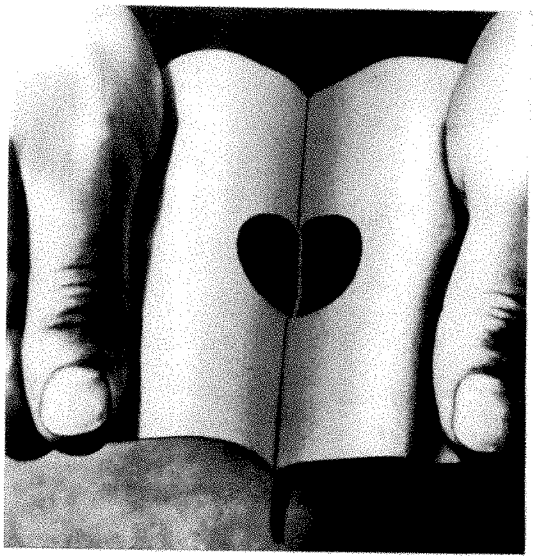

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EDITORIAL CHANGES

It is sad to report that Mr Basil Page, who has done such invaluable work for the *Journal* for some 10 years in the capacity of Assistant Editor, has felt that the time has come for him to retire from this post.

Mr Page has assisted in many editorial functions during his term of Office, but we have been particularly grateful to him for his work on the Index to Current Literature, with Miss Muriel Jones, and for his meticulous management of our various committees.

The pressure of editorial work increases with the years, and the Editorial Committee has thought it necessary to appoint in Mr Page's place two new Assistant Editors, Mr David Essenhigh, Urologist at Newcastle University Hospitals, and Mr W. F. Hendry of St Bartholomew's Hospital and the Institute of Urology. We look forward to their co-operation in many aspects of the work of producing the *Journal*.

D. Innes Williams,
Chairman, Editorial Committee

ANNOUNCEMENT

THE BRITISH ASSOCIATION OF UROLOGICAL SURGEONS TRAVELLING FELLOWSHIP

The British Association of Urological Surgeons is offering a Travelling Fellowship of £250 based on the best paper published in the *British Journal of Urology* in the preceding year including those papers presented at the British Association of Urological Surgeons Annual Meeting.

Authors of papers with multiple authorship should decide which of their number is to receive the Fellowship in the event of their contribution being selected.

Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia or South Africa who are in the course of urological training or who have obtained consultant posts within 10 years of the date of submission of the paper.

Three assessors will be appointed by the Council to make recommendations on the award of the Fellowship. The Council reserves the right not to make an award in any one year.

The award will be announced at the June meeting of the Association.

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Further information may be obtained from Dr H. Thomas, Honorary Secretary of the Urological Society of Australasia, 66 High Street, Randwick, Sydney, New South Wales, 2031, to whom applications with the names of two referees should be forwarded before 1st May 1974.

British Journal of Urology (1974), 46, 3–10

The Single Ectopic Ureter

RICHARD A. MOGG
University Hospital of Wales

Any system of the body which has a complex embryological development is liable to produce anomalous variations of structure, and this is particularly true of the ureter. Furthermore, the close developmental association of the ureter with the genital tract can predispose to the production of many bizarre and complex anomalies. By definition an ectopic ureter must open in the urinary tract at a site between the normal ureteric orifice and the ultimate termination of the Wolffian duct, which is the verumontanum in the male, or at the external urinary orifice in the female. The ectopic ureter is a common anomaly; the majority of ectopic ureters are associated with a pyelon duplex, and this occurs in approximately 75% of cases. On the other hand, the single ectopic ureter is a very rare anomaly, it may be bilateral or unilateral, and it is reputed to occur more commonly in girls though the condition has been described in males.

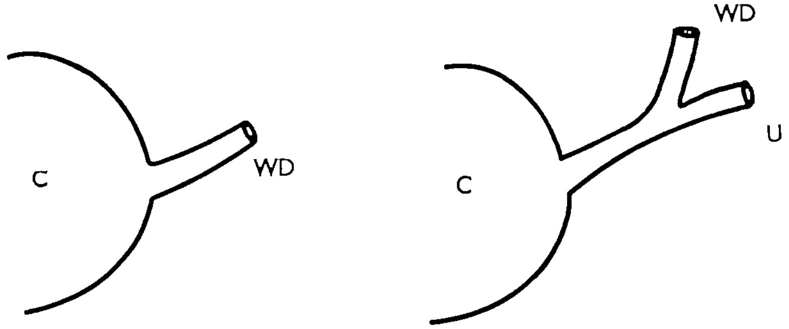


Fig. 1. Ureteric development. C – Cloaca; WD – Wolffian Duct; U – Ureter.

In this presentation 3 cases of ectopic ureter will be discussed: in 1 the anomaly was bilateral, in the other 2 it was unilateral, and it is of interest to note that 2 of the cases occurred in the male (Williams and Royle, 1969). The embryological anatomy of the single ectopic ureter differs markedly from that found in the ectopic ureter associated with a pyelon duplex; these facts will be emphasised later when discussing ureteric development. Therefore, as a result of these developmental differences, the treatment of these 2 apparently similar conditions is completely different.

It is proposed to outline certain aspects of ureteric development applicable to the single ectopic ureter. A fitting time to study the embryology is at the 4 to 5 mm stage (3 weeks) of the developing embryo (Fig. 1) when the paired mesonephric ducts enter the cloaca, and a ureteric bud forms as an outgrowth from the dorsi-medial aspect of the mesonephric duct near its opening into the ventral portion of the cloaca, which will later form the primitive urogenital sinus. This common excretory duct which has now been formed undergoes changes in that the portion of the duct which is caudal to the ureteric bud and dilates, being later absorbed into the wall of the vesico-urethral canal.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

Later, between the 9 and 15 mm stage both ureters and mesonephric ducts should have independent openings into the primitive urogenital sinus, and there now occurs a caudal and medial migration of the mesonephric ducts, and a cranial and lateral migration of the ureter to their ultimate and permanent sites (Fig. 2). The tissue between the 2 orifices of these ducts becomes the adult trigone and trigonal base plate (Fig. 3). Failure of absorption of the caudal portion of the mesonephric duct prevents this normal migration, and this developmental failure prevents formation of the trigone and base plate. Therefore, the mesonephric duct and the ureter must of necessity open in the urethra and the absence of the trigone and base plate produces a wide bladder neck with deformity of the internal sphincter (Cox and Hutch, 1966). Thus, this anomalous development is an important contributory factor in the symptomatology of the single ectopic ureter.

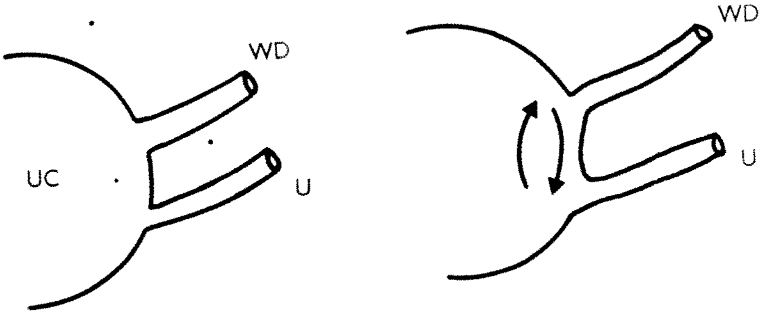


Fig. 2. Development of ureter. UC = Urogenital Canal; WD = Wolffian Duct; U = Ureter.

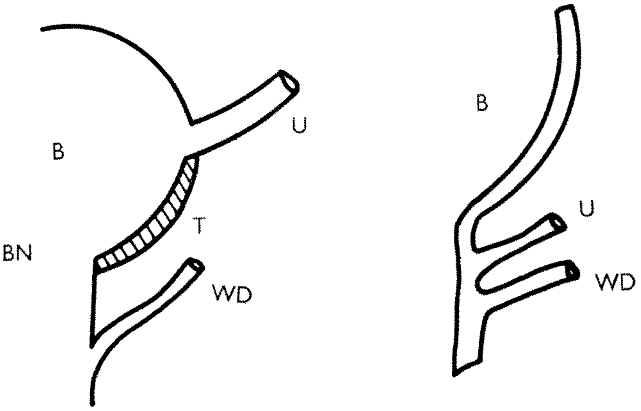


Fig. 3. Development of single ectopic ureter. B = Bladder; BN = Bladder Neck; T = Trigone; U = Ureter; WD = Wolffian Duct.

Incontinence must be a presenting symptom and is the result of 2 factors, primarily due to the fact that both ureters open in an ectopic position in the urethra, and secondly, the abnormal bladder neck mechanism. Furthermore, the bladder is of small capacity as it can contain only urine which has refluxed from the posterior urethra, and therefore can never attain normal proportions. This, of course, is an important factor in treatment because reimplantation of the ureters into the bladder will not cure incontinence, neither will enlargement of the bladder by a colocystoplasty, unless it is possible to reconstruct the bladder neck. The absence of the trigonal base-plate makes the prognosis regarding urinary continence very doubtful, though cases have been recorded where continence has returned. However, in cases where a single ectopic ureter opens in the urethra, associated with a contralateral ureter opening in the normal position, continence will not be affected following the removal of the single ectopic ureter as the hemitrigone which is present in these cases is sufficient to ensure control. The opening of the single ectopic ureter in the male may be in the supramontine portion of the urethra, the ejaculatory duct, the seminal vesicle, or the vas deferens, whereas in the female, the site of termination is most commonly found to be in the urethra or in the vestibule immediately below and behind the urethral meatus.

The most severe and complex form of bilateral single ectopic ureter is seen in association with vesical and urethral agenesis, a very rare condition usually associated with other severe congenital anomalies in the body, often incompatible with life (Fig. 4). The majority of cases are female, incontinence is due to the absence of any form of sphincteric mechanism and the ureters open into the vestigial urethra or at the vestibule (Fig. 5). The majority of these children die, the underlying lesion being usually discovered at autopsy, but of those that survive, ureteric diversion into an isolated intestinal segment is the treatment of choice. Glenn (1959) reports such a case in a Mexican Indian child treated successfully. Only 25 examples of this anomaly have been reported, and the majority have been discovered at autopsy.

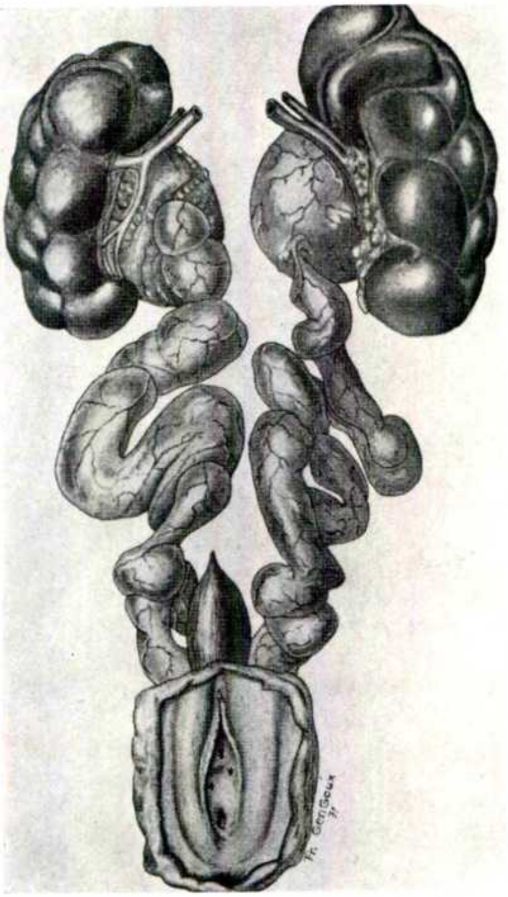


Fig. 4. Vesical and urethral agenesis.

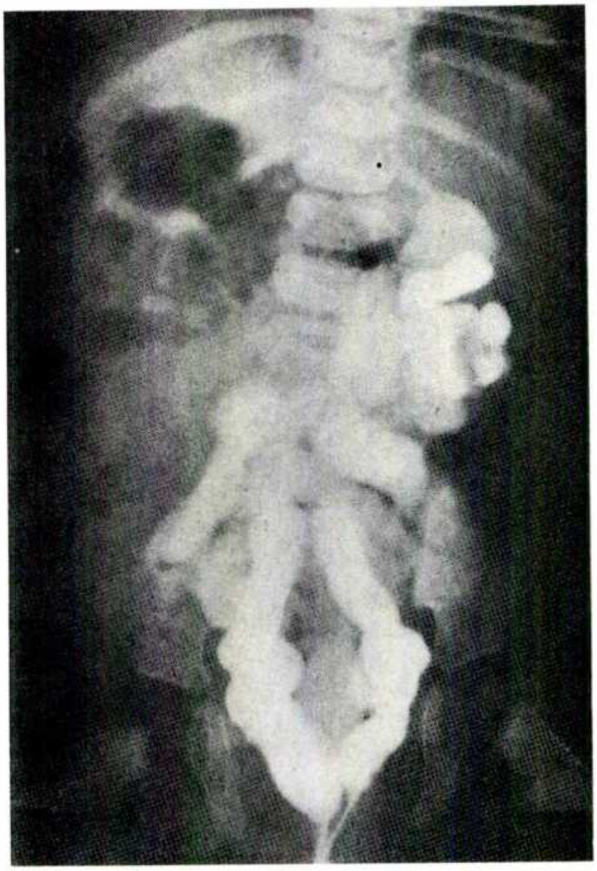


Fig. 5. Bilateral retrograde pyeloureterogram in vesical and urethral agenesis.

In the single ectopic ureter there are structural changes in both the ureter and the renal substance. The ureter is irregularly dilated, the ectopic opening is often stenosed, and there is an associated patchy deficiency in the ureteric muscle due to imperfect development. These factors produce the appearance of pseudo-strictures of the ureteric wall. The changes in the ureteric wall, and the interference with ureteric peristalsis due to the intrinsic abnormalities produce varying degrees of ureteric obstruction with secondary damage to the renal substance. The kidney is often dysplastic which further embarrasses renal function, and there is usually associated chronic pyelonephritis.

It has been reported that in the male when an ectopic ureteric opening is discovered in the genital tract, it is frequently associated with a single ectopic ureter and not with a pyelon duplex as is so frequently assumed; the ureter usually opening in the seminal vesicle (Seitzman and Patton, 1960; Schnitzer, 1965). The presenting symptoms of such a lesion are recurrent infection, painful micturition, perineal and rectal discomfort and epididymitis. Clinical examination may reveal a palpable swelling behind the prostate which in turn produces extrinsic pressure on the lumen of the prostatic urethra. The orifice of the ectopic ureter may be difficult to locate by congenital cystourethroscopy, but micturating cystourethrography readily reveals the site of the orifice or orifices.and, in addition, gives valuable information in respect of bladder capacity and the degree of dilatation of the bladder neck. In the female it is of equal value in demonstrating the site of the ectopic orifice provided that this is in the urethra, and in cases where the ureter opens into the vagina, it is stated that a vaginogram may give valuable information as to its site. However, the value of this investigation is doubtful (Katzen and Trachtman, 1954).

Treatment

In the single ectopic ureter this must of necessity depend on the function of the kidney which it drains, and also of the function of the contralateral kidney if this is present, provided this ureter is not in an ectopic position. In cases of single ectopic ureter, in which a normal contralateral kidney and ureter open normally in the bladder, excision of the affected kidney and ureter by the standard technique of nephroureterectomy is curative. In spite of the fact that this type of anomaly is associated with a hemitrigone, urinary continence prevails. However, in the case of the solitary single ectopic, or bilateral single ectopic ureter, symptoms of incontinence cannot be cured by detaching the ureters from the urethra, and reimplanting them in the bladder. Failure of this operation is due to 2 factors. Firstly, the trigone and the bladder base have never developed and the vital sphincteric mechanism of the bladder neck is absent; also, the bladder neck and posterior urethra are wide open and thus continence is not obtained. Secondly, the bladder has never contained urine except the small quantity which refluxes from the posterior urethra, and its capacity is drastically reduced; also its wall is thin and inert. There have, however, been occasional exceptions and cases have been reported where control has returned though urge incontinence still persists. It is interesting to note that in the third case to be described in this series, the patient had never had any urinary symptoms until urinary infection occurred at the age of 26.

Various plastic procedures have been utilised to restore sphincteric control, but the majority have been unsuccessful, and urinary diversion is usually required to effect a permanent cure (Leadbetter, 1964).

Case Reports

The following cases illustrate many of the typical urological and radiological features of this distressing condition.

C. R., male, aged 5

This child presented with symptoms of incontinence, diurnal and nocturnal since birth. A routine intravenous pyelogram showed only a faint secretion from the left kidney associated with a huge dilated ureter on this side.

On the right side there was evidence of function without dilatation of the ureter (Fig. 6). Micturating cystourethrography showed that both ureteric orifices opened into the posterior urethra and this was later confirmed by cystourethroscopy (Fig. 7). The bladder capacity was reduced, the bladder neck wide and there was funnelling of the posterior urethra with complete absence of the trigone (Fig. 8). A preliminary left nephroureterectomy was performed to remove the functionless left renal unit, and 1 month later a reimplantation of the right ureter into the bladder was carried out. A postoperative micturating cystourethrography showed that the reflux on this side had been corrected, but unfortunately, though the urinary symptoms were less marked, incontinence still persists. It may

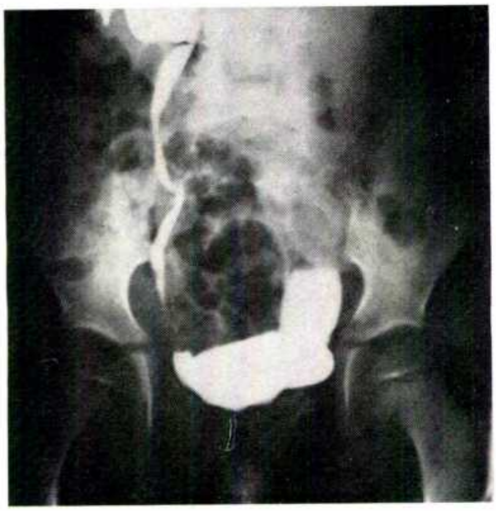


Fig. 6. I.V.P. in patient with bilateral single ectopic ureters.

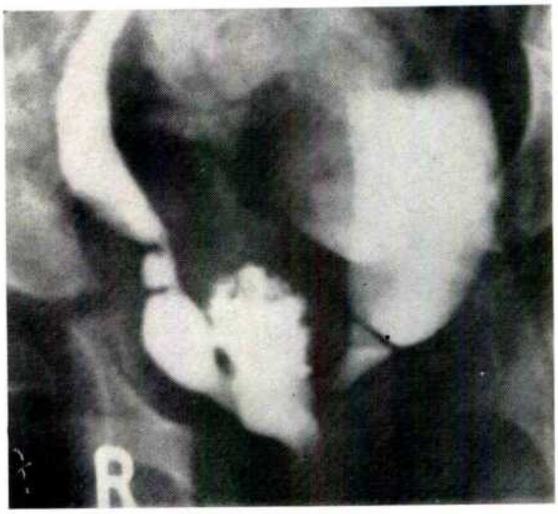


Fig. 7. Micturating cystourethrogram showing termination of bilateral single ectopic ureter.

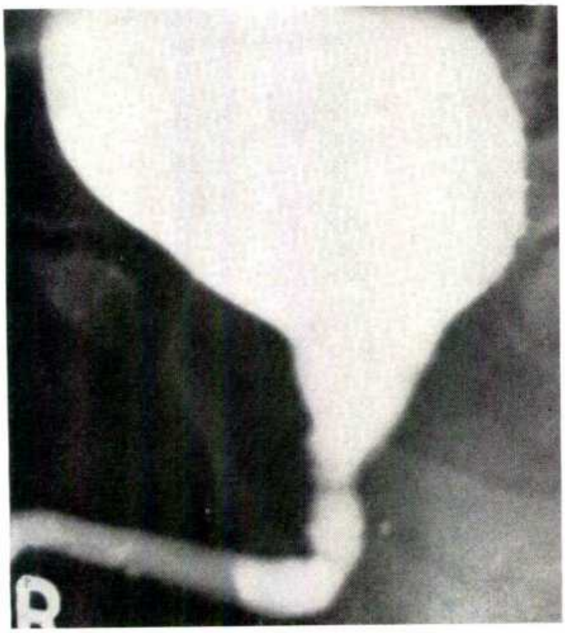
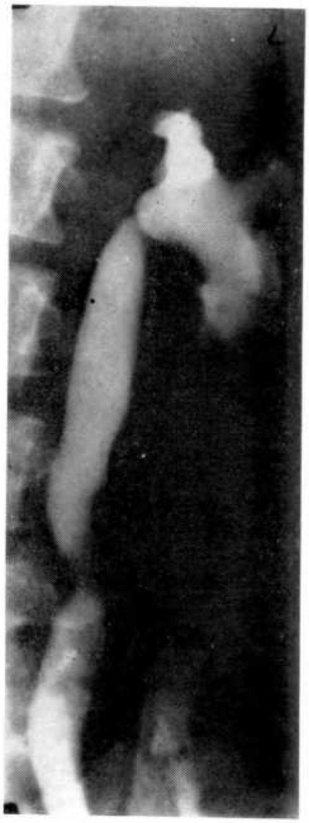


Fig. 8. Cystourethrogram showing wide bladder neck and funnelling of posterior urethra.



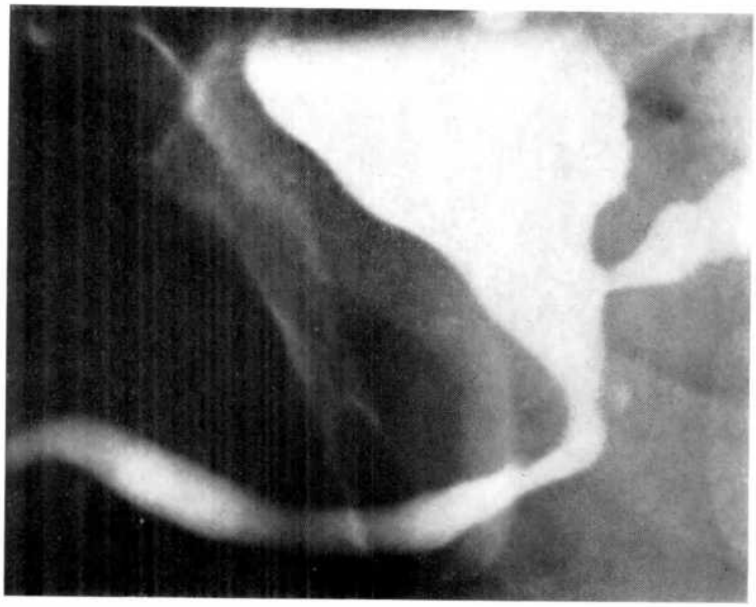


Fig. 9. Cystourethrogram demonstrating total left reflux.

Fig. 10. Cystourethrogram showing site of ectopic ureter.

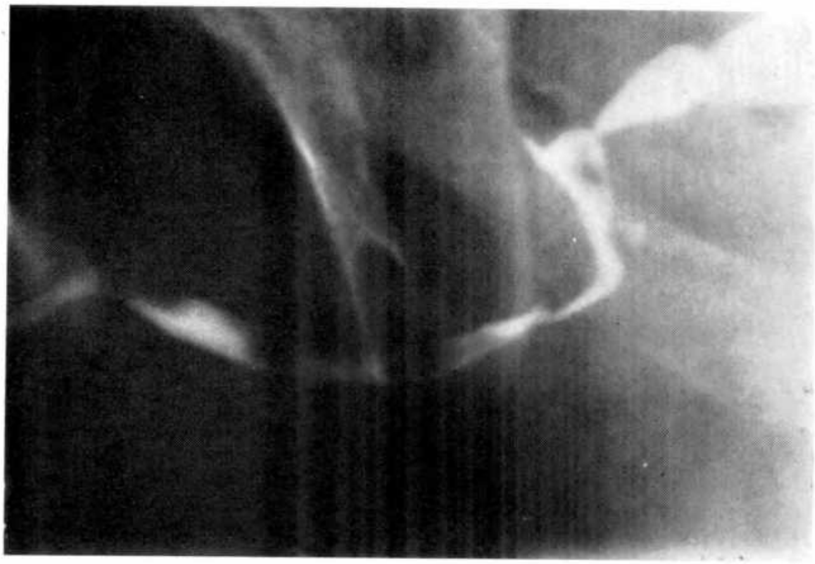


Fig. 11. Cystourethrogram showing solitary ectopic ureter opening at the verumontanum.

be possible to perform some plastic operation on the bladder neck and trigone, but if this is not successful urinary diversion will have to be considered in the not too distant future.

R. J., male, aged 31

This patient was referred for investigation of incontinence which had been present since birth. Apparently at the age of 8 he had been submitted to urinary investigation, when an intravenous pyelogram showed function on the left side with some evidence of hydronephrosis, but no renal shadow or excretion was present on the right side. An exploration of the bladder had been performed without preliminary cystoscopy, and, as far as can be ascertained from the records, it was noted that the bladder neck was dilated, but there was no comment as to the number or the sites of the ureteric orifices. It was recorded that the operative treatment carried out was incision of the dilated bladder neck.

Investigations done on admission showed that the right kidney was absent and that there was very poor function in the left kidney, the pelvis and calyces being dilated, and a micturating cystogram revealed a small bladder with a wide bladder neck, also demonstrating free reflux into a solitary ureter which opened above the verumontanum (Figs. 9-11). Reflux was total, and showed evidence of a regular hydroureter with dilatation of the pelvis and calyces.

Cystourethroscopy confirmed these findings: there was a small ectopic opening in the posterior urethra above the verumontanum, the right ureteric orifice was not visualised, either in the bladder or in the posterior urethra, and there was complete absence of the trigone. A diagnosis of a single ectopic ureter with contralateral renal agenesis was established. A rapidly rising blood urea associated with signs of renal failure and hypertension justified urinary diversion in this patient, and a permanent ureterostomy was established on the left side. He was well maintained for a short period following this operation, but progressive renal failure necessitated intermittent dialysis which was commenced in May 1971. The patient has been satisfactorily maintained by this method and is alive and relatively well.

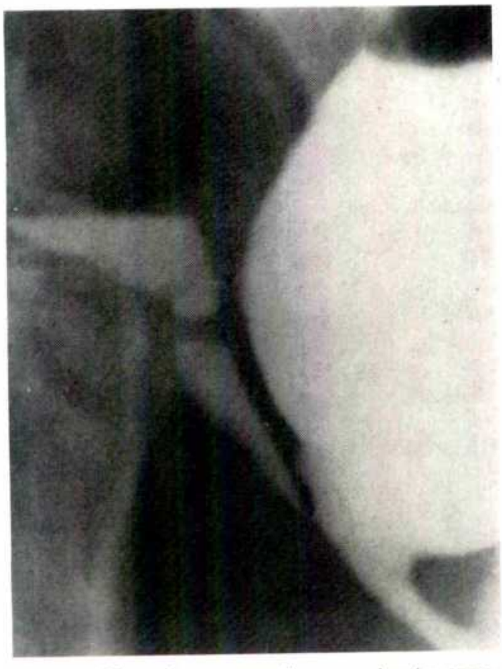


Fig. 12. Micturating cystourethrogram showing opening of single ectopic ureter.

K. W., female, aged 26

This young nurse in training had been perfectly fit and well all her life until she had an acute urinary infection with an associated *B. coli* septicaemia. Investigation of the urinary tract when the presenting symptoms had subsided showed left renal agenesis, and the kidney on the right side showed gross hydronephrosis and hydrocalycosis. The ureter was not visualised. Cystourethroscopy failed to identify any ureteric orifice and it was noted that there was a complete absence of the trigone. However, there was a small stenosed opening of the ectopic right ureter in the proximal urethra, and it was possible to catheterise this ureter for a distance of only 2 cm. Complete obstruction was encountered at this site.

A micturating cystogram revealed a solitary ectopic ureter on the right side opening into the proximal portion of the urethra. The ureter showed asymmetrical dilatation with free reflux to the kidney (Fig. 12). At operation the single ectopic ureter was detached from its opening into the urethra; it was found to be grossly dilated above a stenotic segment situated some 3 cm from its opening and, therefore, it was necessary to taper the ureter in order to reduce its lumen before reimplantation into the bladder by the Leadbetter-Politano technique could be performed. The postoperative course was uneventful and she has remained fit and well since surgical intervention, but unfortunately a repeat micturating cystogram shows that there is some reflux into the ureter though this is not total. She has remained free of infection, and it is proposed to treat her on conservative lines for the time being.

Summary

The embryology of the single ectopic ureter is discussed. 3 cases of single ectopic ureter, 1 bilateral and 2 unilateral, are described together with the methods of investigation and treatment.

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British Journal of Urology (1974), **46**, 11–14

An Aggressive Approach to Stones in the Lower Ureter

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The probability that a ureteric stone will pass spontaneously is closely linked to the size of the stone. The figures most commonly quoted are those of Sandegård (1956) indicating that the critical size is about 4 mm. Below 4 mm, over 90% of the stones in the lower ureter and 80% of stones in the upper ureter will pass spontaneously, whereas at 4 to 6 mm only half of the stones in the lower ureter and one-fifth of those in the upper ureter will pass. When the stone is larger than 6 mm the chances of spontaneous passage scarcely justify expectant treatment—although we are all aware of startling exceptions. The stone in the lower right ureter shown in Figure 1 had the approximate dimensions of a cigarette. It was passed spontaneously 2 weeks after this X-ray was taken.

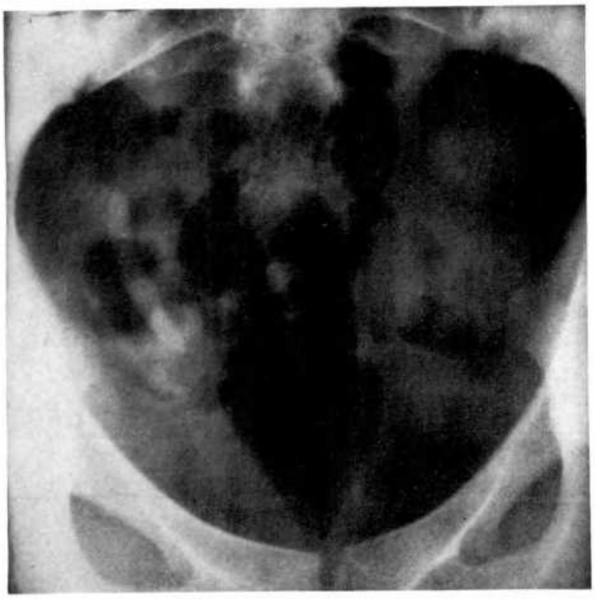

Fig. 1

When first seen, nearly 80% of stones are in the lower third of the ureter and it is these that give rise to most argument. If the patient remains completely symptom free after his first attack of renal colic has been relieved and if there is no serious obstruction it is obviously reasonable to wait and watch, but very many patients are not symptom free. In my experience it is the very

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small stones that cause the most pain. I do not think it is reasonable that an otherwise healthy patient with recurrent pain should be asked to wait days and weeks with the threat of renal colic hanging like a sword of Damocles over his head. When the stone is not moving and there is recurrent pain, I believe that the patient should be offered the relief of endoscopic extraction at an early stage.

Councill (1945) reported a series of 504 cases with successful extraction in 70% but, impressive as these figures were, the profession was even more impressed with the risks. Councill reported 3 ruptured ureters and 2 cases of septicaemia and 2 of his patients died. Ellik and Newton (1951) were equally frank. Their procedure involved traction on an Ellik loop, a somewhat unpleasant procedure for the patient. They had 4 ruptured ureters with 1 nephrectomy and 1 death in a series of 74 cases.

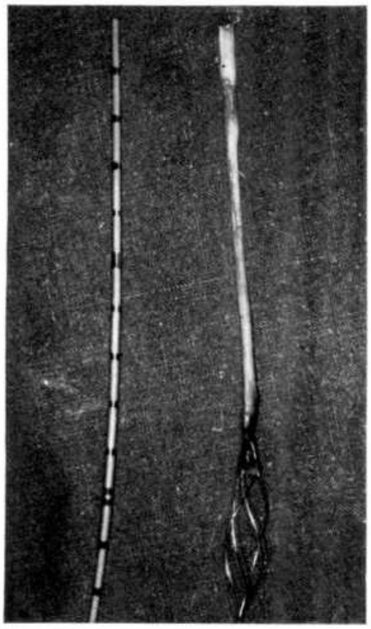

Fig. 2

Table I

Complications in 234 Endoscopic Procedures

Technique	Torn Ureter	Basket Stuck	Pain and Fever for 2 Days
Loop (16)	1	...	...
Basket (218)	1	2	8

Table II

Ureteric Stone Endoscopic Procedure—161 Cases

Technique	Total	Immediate Success (%)	
Loop	16	3 (19%)	
Councill basket	10	3 (30%)	
Dormia basket	126	82 (65%)	67·4%
Endoscopic ureterolithotomy	9	9 (100%)	

Rightly, risks of this order were considered unacceptable. The introduction of the Dormia basket in the 1950s seemed to promise a new safety in transurethral manipulation of stones but soon there were whispered horror stories of disasters. Any instrument misused may be lethal. I believe that properly used the Dormia basket is safe and effective. The basket should not be used on large stones. Except in the hands of very experienced operators it should be used only in the lower third of the ureter. It should not be used when there is a combination of ureteric obstruction and acute infection, as indicated by fever and loin tenderness. The surest recipe for disaster is to give a tug if the basket sticks. Figure 2 illustrates such a disaster. The basket stuck on a 5-mm stone just above the ischial spine. Four pounds traction was applied for 24 hours and then a moderate tug brought away basket, stone and 9 cm of ureter. The rule must be absolute: if the basket sticks above the intramural ureter a fold of ureteric mucosa has probably been caught between basket and stone. In this situation it is imperative not to apply the slightest force but to proceed to open surgery.

Certain technical details are important. If a right-angle cystoscope is used, the deflecting bar may be left in the "up" position and interfere with the very essential sense of touch. It is preferable to use a foroblique or direct vision cystoscope so that the basket will run freely through the instrument. As the manufacturers advise, when the basket has passed the stone it should be pushed up 1 cm and pulled down 2 cm, up 1 and down 2 and so on and it is a mistake to try to close the basket on the stone. When the basket successfully gathers the stone it will commonly stick in the intramural ureter, but provided that at least half of the basket is visible in the bladder it is perfectly safe to pull as hard as is necessary to get the stone out. In my own series of 126 stones extractions using a Dormia basket, a particularly vigorous pull on a stone stuck in the intramural ureter was recorded in 11 cases, without any complication, early or late.

Table III

Failed Dormia Extraction Subsequent Fate of 44 Cases

Stone passed		
in 1 week (1, 4, 4, 2, 0, 2, 1)	14	
in 2 weeks	5	
in 4 weeks	4	
in 6 weeks	1	
	—	24
Basket stuck—immediate open surgery		2
Elective open surgery		8
Vaginal ureterolithotomy		2
Endoscopic ureterolithotomy		1
Not recorded		7
		—
Total		44

Table IV

(Butler and O'Flynn, 1973)

Technique	Total Number	Stone passed within 6/52
Catheter	70	15
Dilatation	13	3
Basket	(77 − 23) = 54	42

Figures taken from the paper by Butler and O'Flynn (1973). A stone basket was passed on 77 occasions, removing the stone in 23—in the 54 remaining cases, the stone passed within 6 weeks in 42.

If the stone presents in the intramural ureter and can be seen at cystoscopy, either bulging into the bladder or peeping out of the ureteric orifice, I believe that a basket should not be used at all. Recent articles (Barnhouse *et al.*, 1973; Landes, Gavigan and Fehrenbaker, 1973) advocate open transvesical ureterolithotomy in this situation, but in my view this is unnecessary because *transurethral* ureterolithotomy, cutting directly on to the stone with a knife electrode is a very simple and uniformly successful procedure. If the stone is in the upper part of the intramural ureter it is helpful to place a ureteric catheter in the ureter as far as the stone to act as a guide to the correct line of incision.

Before considering results in terms of stone removal it is important to consider complications because if the procedure is to be acceptable it must be safe. Table I shows the total complications in 234 endoscopic procedures, including cases in which the ureter was dredged because the diagnosis was uncertain but ultimately proved to have no stone. The Ellik loop was used in 16 cases and in 1 failed case at subsequent open operation the ureter was found to have been torn for 2 cm above the stone. This can happen easily if the loop is not perfectly closed. In 218 cases where a Dormia basket was used there was 1 torn ureter (already described). The basket stuck in 2 and both cases were easily dealt with by open surgery. Only in 8 patients was there significant pain and fever for 2 days.

Table II shows the immediate success rate in a consecutive series of 161 cases. It will be noted that the overall immediate success rate with the "modern" techniques using either a Dormia basket or endoscopic urethrolithotomy was 67·4%.

Table III shows what happened in the 44 cases in which extraction failed. In 24 the stone was passed within 6 weeks, 11 of these in the first 4 days.

It is sometimes claimed that one can equally induce passage of the stone simply by passing a catheter beyond the stone or by dilating the ureter by passing two 5F catheters beyond the stone but Butler and O'Flynn (1973) have produced striking evidence to the contrary (Table IV).

Summary

In cases of stone in the lower ureter, a conservative attitude should be adopted only if the patient is symptom free and there is no significant ureteral obstruction.

Properly used, the Dormia basket is a safe and effective instrument.

In a consecutive series of 126 cases of stone in the ureter where the Dormia basket was used, the stone was extracted immediately in 82 (65%).

When the stone is stuck in the intramural ureter it should be removed by transurethral ureterolithotomy.

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Experimental Ureteric Obstruction

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It is now established that glomerular filtration continues after ureteric obstruction (Taylor and Ullman, 1961; Salomon and Lanza, 1962; Selkurt, Deetjen and Brechtelsbauer, 1965). Tubular reabsorption continues in both proximal and distal parts of the nephron (Malvin, Wilde and Sullivan, 1958). Renal blood flow increases initially (Selkurt, 1963; Harsing, Szántó and Bartha, 1967; Wax, 1968; Navar and Baer, 1970; Carlson and Sparks, 1970; Suki *et al.*, 1971; Honda *et al.*, 1971) but later declines (Murphy and Scott, 1966; Vaughan, Sorenson and Gillenwater, 1968).

The normal resting proximal tubular pressure in the rat is raised during diuresis (Gottschalk and Mylle, 1957; Falchuk *et al.*, 1971). Proximal tubular pressure is also raised following ureteric obstruction and a further increment occurs during simultaneous ureteric obstruction and diuresis (Gottschalk and Mylle, 1956; Selkurt *et al.*, 1965). Struthers (1969) found raised renal pelvic pressures during diuresis in the dog. Bretland (1972) in his review of the literature on ureteric obstruction concluded that "actual pressure achieved seems to depend on the degree of diuresis and varies from 40 to 75 mm Hg in the dog".

Nephron damage following ureteric obstruction has been shown to be proportional to the pressure applied (Selkurt, Brandfonbrener and Geller, 1952; Wax, 1968; Honda *et al.*, 1971). This series of experiments was designed to examine whether hydration during ureteric obstruction, in the rat, would influence nephron recovery after a short (less than 2 hours) and long (6 hours) period of ureteric obstruction.

Method and Results

Short-term Obstruction

In the first series of experiments, hydrated and dehydrated groups of rats were studied. The hydrated group of animals received an intravenous infusion of 0·3% NaCl at 5 ml/hr and the ureter was obstructed for 75 minutes. The dehydrated group received a maintenance infusion of 0·8 ml/hr of 0·3% NaCl. Ureteric obstruction was prolonged to 90 to 120 minutes in this group as the initial rise of ureteric pressure was slow due to the dead space of the pressure transducer relative to urine flow rate.

End ureteric pressures (Fig. 1) of the diuretic series (8 rats) reached a steady level at 53 mm Hg whereas in the antidiuretic series (9 rats) the pressure level was 27 mm Hg. These differences were highly significant ($P < 0{\cdot}001$).

In the hydrated series (7), urine volumes (Fig. 2) in control periods prior to obstruction showed little difference between the control and the experimental kidney ($P > 0{\cdot}8$).

After release of the obstruction in the hydrated group there was a prompt washout of urine from the renal pelvis and ureter. However, the urine flow rate continued at higher rates from the experimental kidney than from the control for 1 hour after release. Differences were significant ($P < 0{\cdot}05$) during the period 10 to 40 minutes following release.

In the dehydrated series (5 rats) during the 30-minute control period prior to obstruction, experimental and control urine flow rates were similar ($P > 0{\cdot}7$) (Fig. 3). For 30 minutes after

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release of obstruction the urine flow rate from the experimental kidney was greater than from the control but the differences were significant for only 0 to 15 minutes following release (P <0·05).

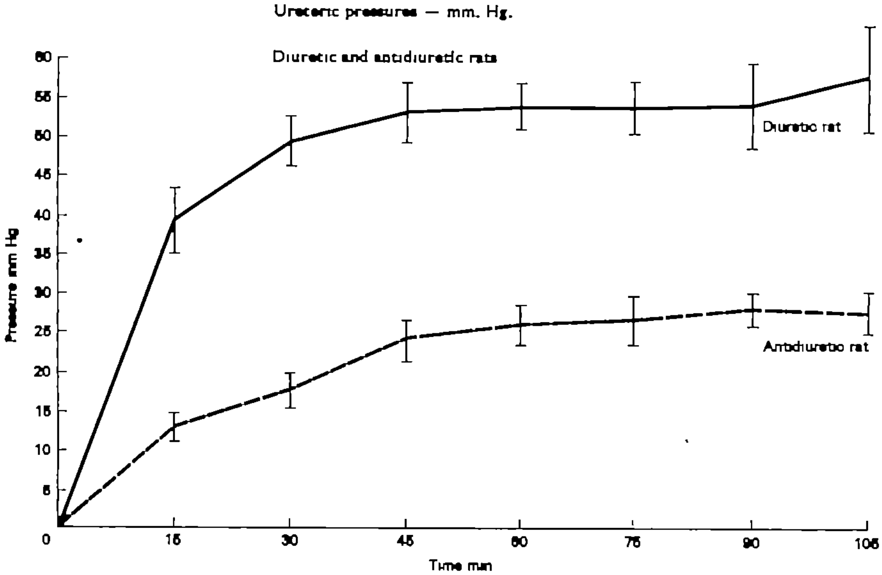

Fig. 1

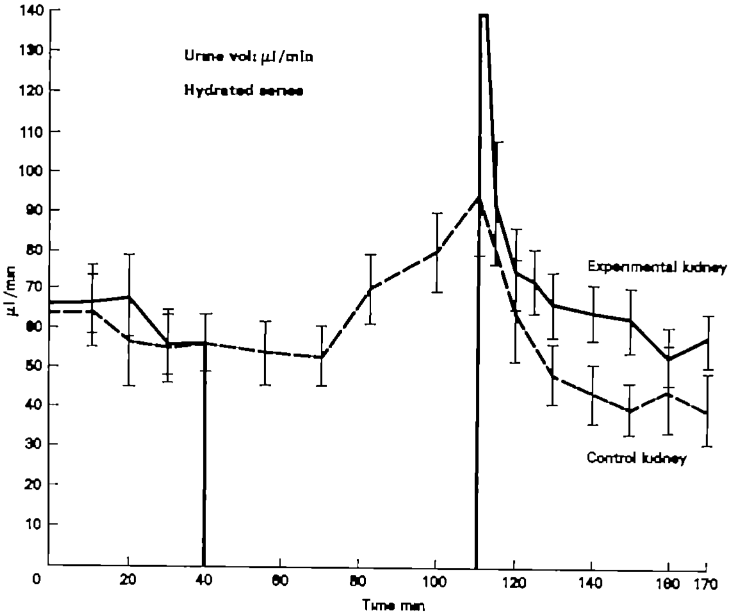

Fig. 2

In the hydrated series (7 rats) and the dehydrated series (5 rats) there was no significant difference in osmolality between the urine of the experimental and the control kidneys prior to ureteric obstruction.

In the hydrated series from 5 to 60 minutes (Fig. 4) after release of obstruction, the experimental kidney urine was hypotonic compared to the control urine (P <0·025). In the dehydrated series urine osmolality was significantly less than in the control ($P < 0{\cdot}05$) from 0 to 30 minutes only (Fig. 5).

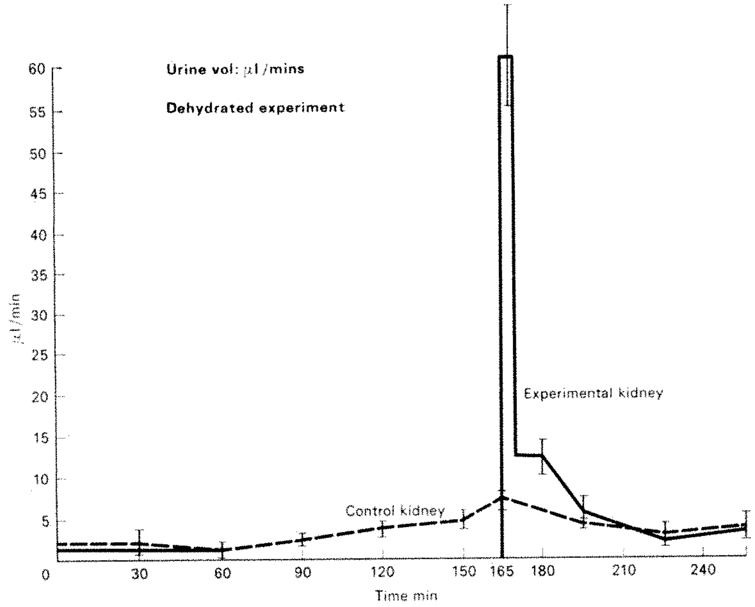

Fig. 3

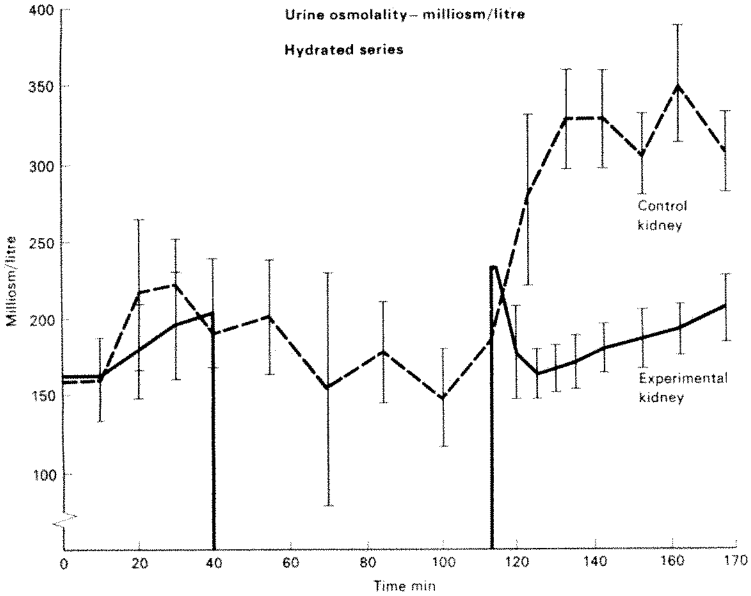

Fig. 4

No significant difference was seen in inulin clearance after release of obstruction in the hydrated series (4 rats).

Urinary sodium concentration (7 rats) was lower in the postobstructive kidney of the hydrated

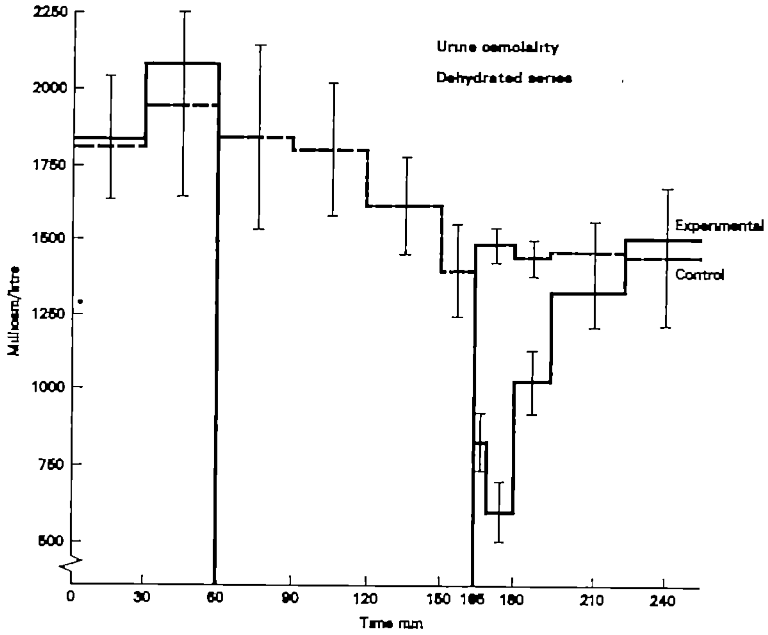

Fig. 5

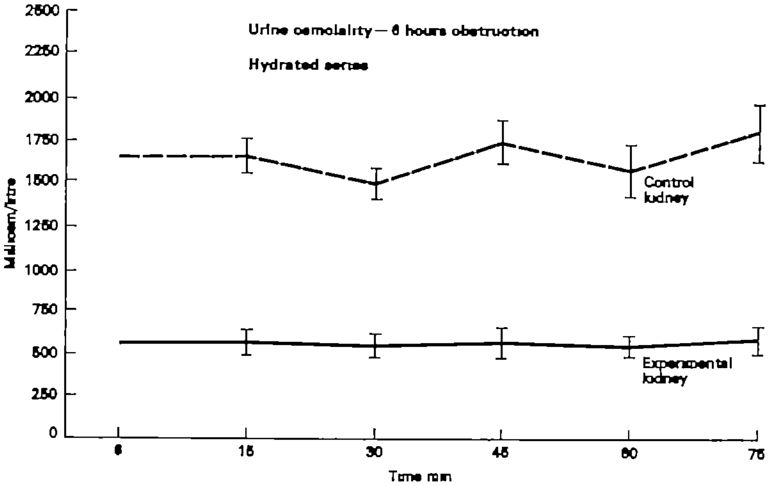

Fig. 6

series compared with the control. Urinary sodium excretion was, however, greater from the experimental kidney although none of these findings was statistically significant.

6-hour Obstruction

In the second series of experiments, rats had 1 ureter tied during a light ether anaesthetic and the animals were allowed to recover. One group was hydrated (10 rats) with a stomach load (5% body weight) of water and in the second dehydrated group (8 rats), water was withheld. In both groups, ureteric obstruction was released after 6 hours and nephron function then assessed. Measurements were made at 15-minute intervals from 6 minutes after release of obstruction.

Whilst no significant difference was seen between urine volume of experimental kidneys, urine osmolality from the experimental kidneys (Figs. 6 and 7) was significantly less than from the control ($P < 0{\cdot}01$). The difference was greater in the dehydrated group owing to previous dehydration of the animal.

Glomerular filtration was measured by the clearance of inulin. The average control kidney inulin clearance was 0·5 ml/min for both groups. Experimental kidney inulin clearance was 0·12 to 0·15 ml/min in the hydrated group (10 rats) and 0·3 to 0·35 ml/min in the dehydrated group (8 rats). The differences between the experimental kidney inulin clearances in the 2 groups are expressed as a ratio of control kidney inulin clearances (Fig. 8). The ratio of control kidney and experimental kidney inulin clearances are significantly greater for the hydrated series at 15, 30 and 60 minute collections ($P < 0{\cdot}05$).

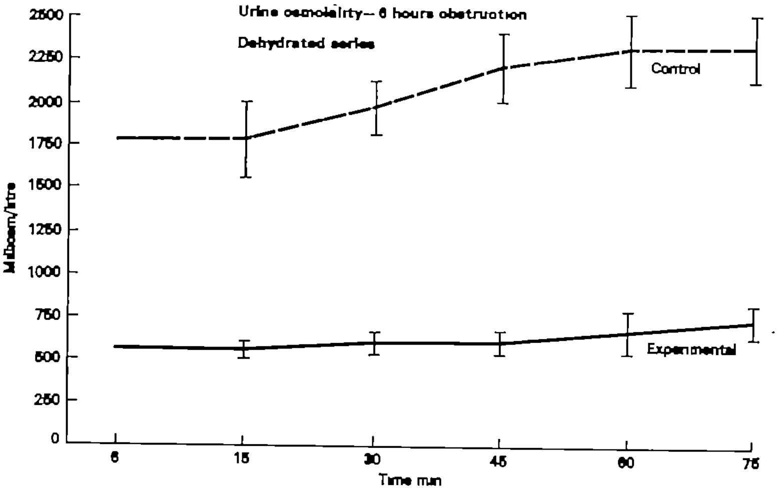

Fig. 7

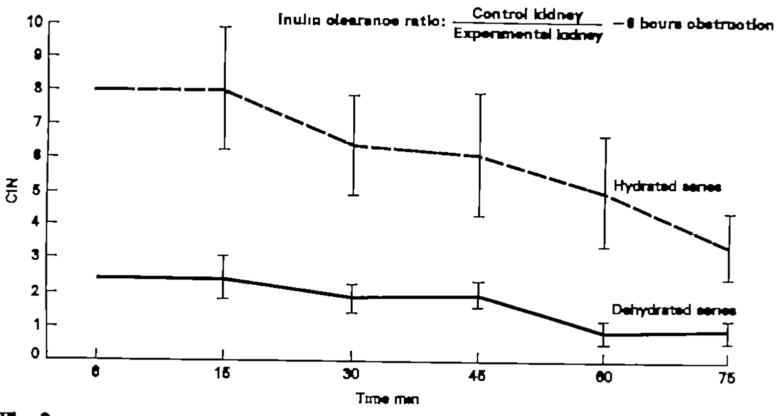

Fig. 8

Sodium concentration alone showed no marked difference between the 2 groups. However, when sodium excretion was related to the inulin clearance $\left(\frac{\textit{Sodium Excretion}}{\text{G.F.R.}}\right)$ a sodium loss was seen from the experimental kidney, which was greater in the hydrated series (Figs. 9 and 10).

Discussion

Urine osmolality proved a sensitive index of nephron damage after both short-term (less than 2 hours) and 6-hour obstruction. This confirms osmolar changes described by Jaenike and Bray (1960), Kessler (1960), Selkurt (1963) and Finkle, Karg and Smith, (1968). Urine osmolality shows greater nephron damage in the hydrated kidney after short-term obstruction compared to the dehydrated low-pressure group. The production of hypotonic urine and free water clearance in the postobstructive hydrated kidney makes washout of the corticomedullary gradient unlikely to be the entire explanation. Urinary sodium excretion was greater in the postobstructive kidney of the hydrated series despite the hypotonicity. This natriuresis combined with the natriuresis/G.F.R. seen in the 6-hour obstructed kidney suggests a proximal tubular damage with overload of distal tubular capacity agreeing with Bercovitch *et al.* (1971). Yarger, Aynedjian and Bank (1972), from micropuncture evidence, after 24 hours' ligature in rats thought distal nephron damage to be more important. However, of necessity, routine micropuncture only measures superficial nephrons and from loss of total G.F.R. the authors concluded there was greatest damage in deep nephrons.

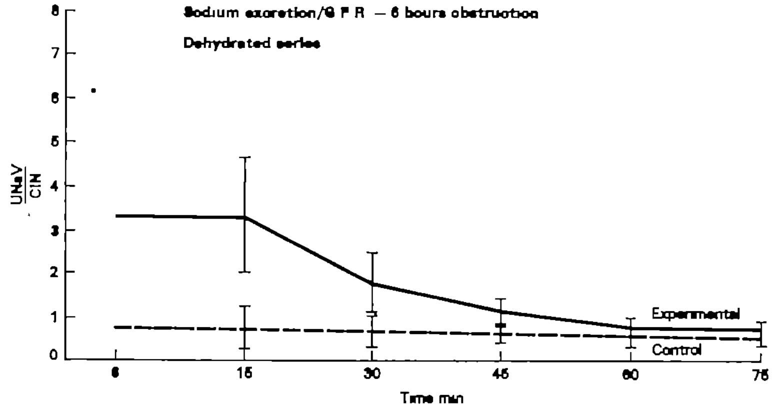

Fig. 9

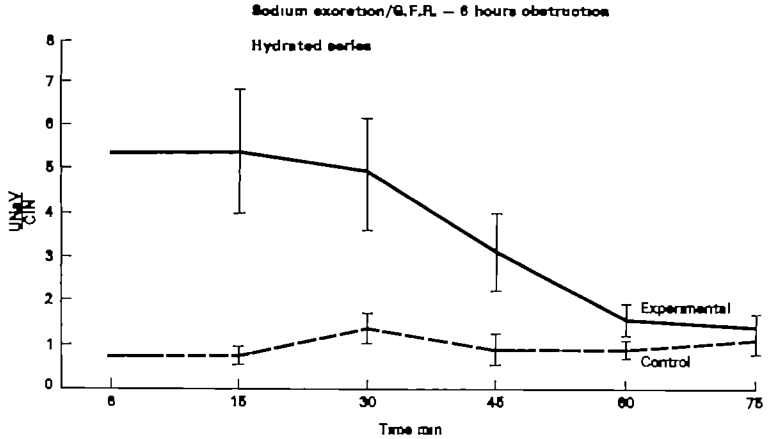

Fig. 10

After 6 hours' ureteric obstruction, inulin clearance was significantly reduced in the experimental kidney of the hydrated compared to the dehydrated group. During ureteric obstruction important changes to non-reabsorbed solutes and the usual filtration markers have been reported (Lorentz, Lassiter and Gottschalk, 1972). This explains the reduced residual filtration after ureteric obstruction in mannitol diuresis (Taylor and Ullman, 1961; Selkurt *et al.*, 1965).

In no experiments were osmotic diuretics used. Loss of G.F.R. following 6-hour obstruction may be due to each nephron filtering at a decreased rate, but previous evidence suggests a decreased nephron population (Malvin, Kutchai and Ostermann, 1964; Jaenike, 1972).

Increased ureteric end pressures and greater nephron damage in the hydrated series may be due to higher renal plasma flow and G.F.R. in the volume-expanded rat causing greater load to the occluded nephron: secondary to a fall of renal afferent arteriolar resistance (Brenner *et al.*, 1972). Proximal tubular reabsorption may be decreased in the hydrated animal secondary to a fall of peritubular capillary protein, and a rise of peritubular hydrostatic pressure (Brenner *et al.*, 1969; Brenner *et al.*, 1971; Brenner, Troy and Daugharty, 1972). The action of a natriuretic hormone is also possible.

In hydration, A.D.H. secretion is minimal and thus distal nephron permeability is low. Interesting is the previous suggestion of minimal osmolar changes when A.D.H. was given during obstruction (Kessler, 1960; Suki *et al.*, 1971).

Finally, during hydration the escape route of either pyelolymphatic or pyelovenous shunts may be overloaded.

Relevance to human renal physiology may be questioned. In particular, G.F.R. and renal blood flow are constant in man during diuresis (Pitts, 1968). However, much of human renal physiology is based on animal experimentation and it is possible that during ureteric obstruction the human kidney resembles the phylogenetically simpler rat. In support of the experimental work is the increase of pain following diuresis during ureter obstruction in man (Weaver, 1968). It is suggested therefore that in clinical work possibly greater nephron damage during partial or total ureteric obstruction following hydration should be considered. It is accepted, however, that a policy of restricting fluids may require modification in patients with recurrent stone formation secondary to high urinary concentration of inorganic compounds.

Conclusions

(i) Obstructed ureteric end pressures are significantly greater in hydrated rats.
(ii) Release after less than 2 hours' obstruction shows nephron recovery as shown by urine osmolality to be greater in lower pressure dehydrated rats.
(iii) Release after 6 hours of ureteric obstruction in rats showed:
  (*a*) Urine osmolality was significantly decreased in both hydrated and dehydrated groups.
  (*b*) Inulin clearance of experimental kidney was lower in hydrated series.
  (*c*) Natriuresis/G.F.R. was greater in hydrated series.
(iv) In clinical work possibly greater nephron damage during partial or total ureteric obstruction following hydration should be considered as well as concentrations of bacteria or inorganic compounds.

Summary

Renal function during and after release of a short period (less than 2 hours) and following release of a long period (6 hours) of total ureteric obstruction in the rat was studied in 2 series of experiments.

Ureteric end pressures were found to be significantly higher in diuretic compared to dehydrated rats in the short period series of experiments. In both series of experiments nephron recovery following release of ureteric obstruction was greater in dehydrated compared to hydrated rats.

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The reasons for the difference of results in hydrated compared to dehydrated rats and sites of nephron damage are discussed.

Possible relevance to clinical work is also propounded.

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Electromyography of the Detrusor, A Method of Investigation of Normal and Abnormal Detrusor Function

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Current methods of investigation enable one to divide patients suffering from urodynamic problems into several broad groups: those with defective sphincters, those with some abnormality of the detrusor, and those with both sphincter and detrusor dysfunction. The purpose of this paper is to evaluate the place of detrusor and sphincter electromyography in the diagnosis and investigation of these patients.

Materials and Methods

The Incontinence Unit at the Institute of Urology has been investigating patients with persistent urodynamic problems since 1967. We have been using conventional diagnostic methods including urethral pressure profiles and cystometrograms with X-ray studies. We have found the results of the urodynamic investigations occasionally difficult to interpret. When a cystometrogram is being done some patients will allow only a small volume of fluid to be infused into the bladder, so that little information is gained. In other cases there are bizarre pressure changes that do not fit into any accepted pattern. In an attempt to gain further basic information about bladder and sphincter function, and to investigate more objective methods of assessment, we have done electromyographic studies on selected patients. The investigations have been carried out on conscious female out-patients. We have inserted electrodes through the anterior vaginal wall, hooking them into the trigonal area of the bladder. This technique has been described by Stanton, Hill and Williams (1973). We have then simultaneously recorded electromyographic activity from the detrusor, urethral and anal sphincters and have monitored bladder and rectal pressure. We have measured urine volume and flow rate, and recorded the pulse and respiratory wave forms to determine their effect on the tracings. The patients sat on a specially adapted commode, and were encouraged to drink a fluid load. The recordings were made in a separate room, the patients being observed on closed-circuit television to allow as much privacy as possible.

Results

We have studied 53 cases up to the present time without any serious complications. The nature of the investigation was fully explained to the patients; none of them refused consent to have the investigations. This paper presents the results in 27 patients.

We investigated 3 normal patients. In these cases there was low-frequency detrusor activity in waves of up to 500 microvolts amplitude, with a frequency of 0·5 to 5·00 Hz (Fig. 1). This activity increased in amplitude prior to micturition. The waves were random in nature, similar but lower

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in frequency to the pattern seen on an E.E.G. The wave forms did not seem to change with variation of bladder pressure or bladder volume. The anal and urethral sphincters in these 3 cases gave recordings in the 50 to 100 microvolt range with a frequency of 0·5 to 15 Hz. During bladder filling there was some increase in sphincter activity to 150 microvolts amplitude. In 2 of these cases there was diminution of the amplitude of both sphincters with micturition.

There were 11 cases of detrusor dysfunction. Among these there were 4 cases of neuropathic bladder due to multiple sclerosis. Of the 11 cases, the most active showed a continuous spiky activity with a fundamental frequency in excess of 15 Hz. They also showed large low-frequency waves of 1,000 microvolts or more (Fig. 2). There were 3 cases in whom a diagnosis was made of a hypotonic detrusor. Here there was little change in the high- or low-frequency activity from the pattern seen in the normal patient, but we recorded activity from the dome region of the bladder in these 3 cases, by passing wires suprapubically into the detrusor muscle (Fig. 3). The activity at the dome differed in that the wave form was increased in frequency from 0·1 to 0·17 Hz in 2 cases while in the 3rd case there was less activity in the trigonal region of the bladder. In 10 cases there were electromyographic abnormalities of both sphincters and detrusor.

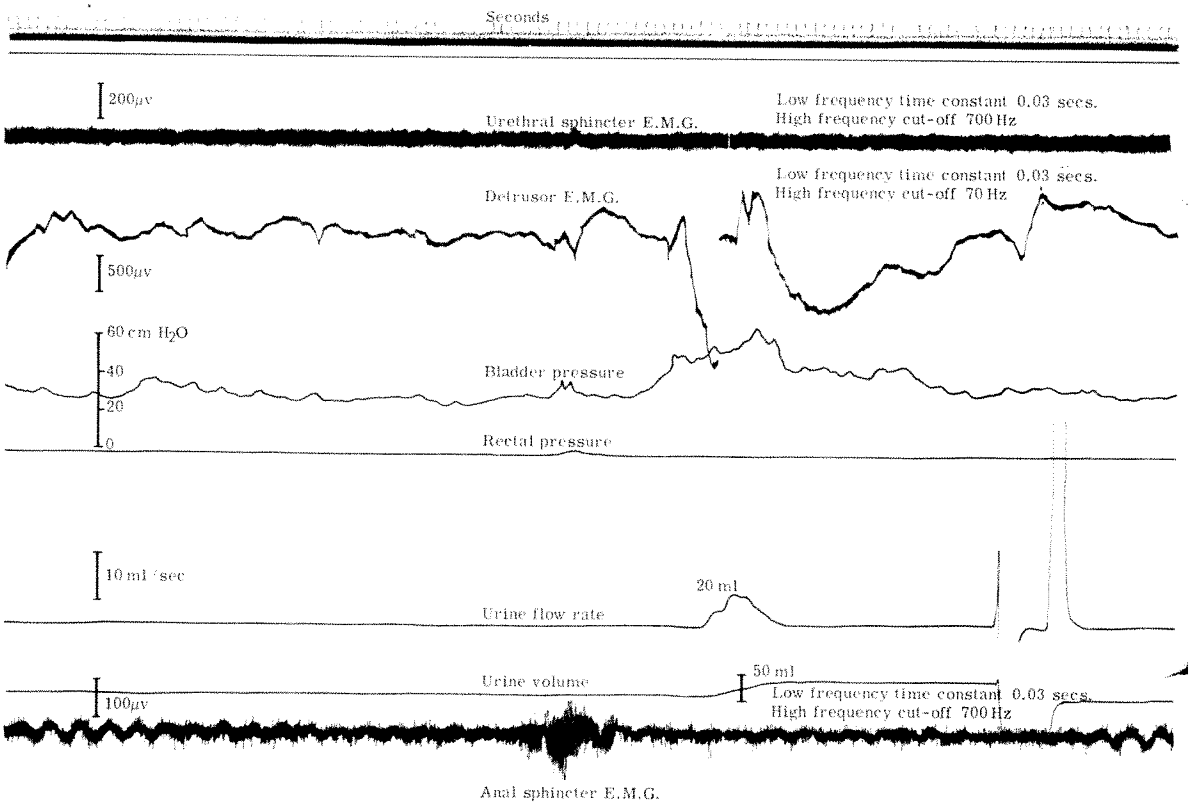

Fig. 1. Normal low-frequency detrusor E.M.G.

We attempted to diagnose the patient's bladder function from the E.M.G. and pressure tracings alone, without using the results from the more conventional tests. Of the 27 cases reported, there was good correlation in the diagnosis of detrusor function in 15 cases. We were unable to show any abnormality in the detrusor E.M.G. in the cases suffering from multiple sclerosis, and we feel that in this disease more investigation is required. If these cases are excluded, there was good

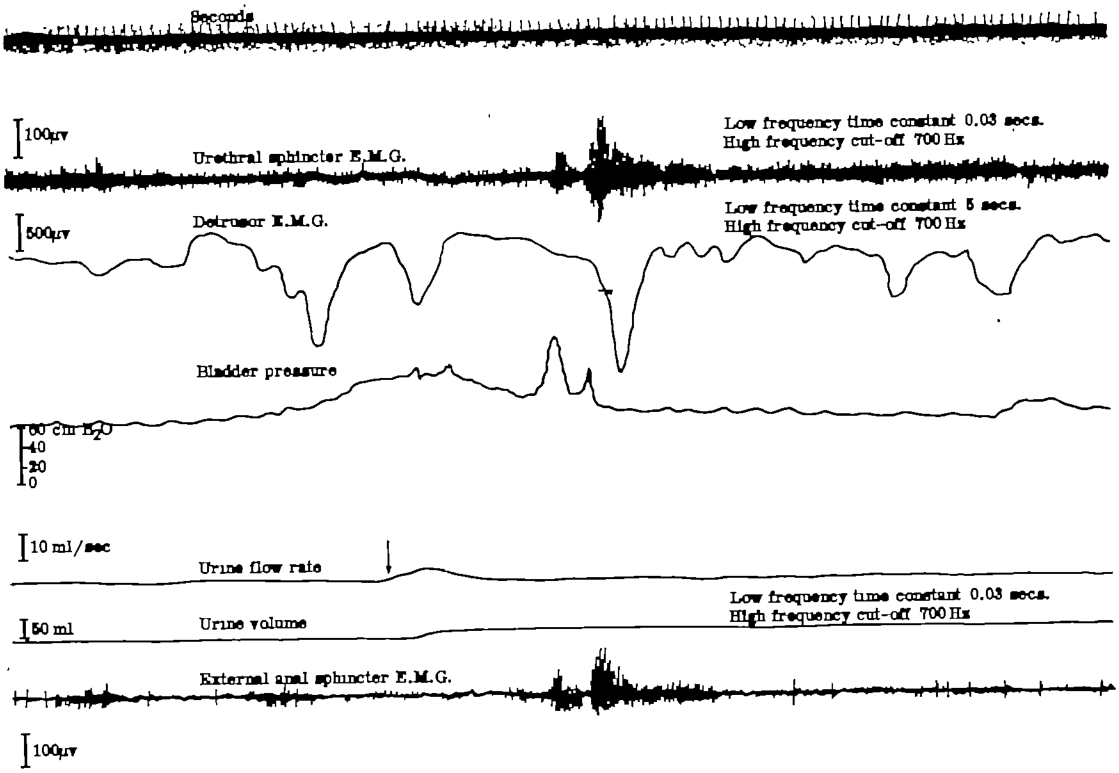

Fig. 2. Overactive detrusor E.M.G.

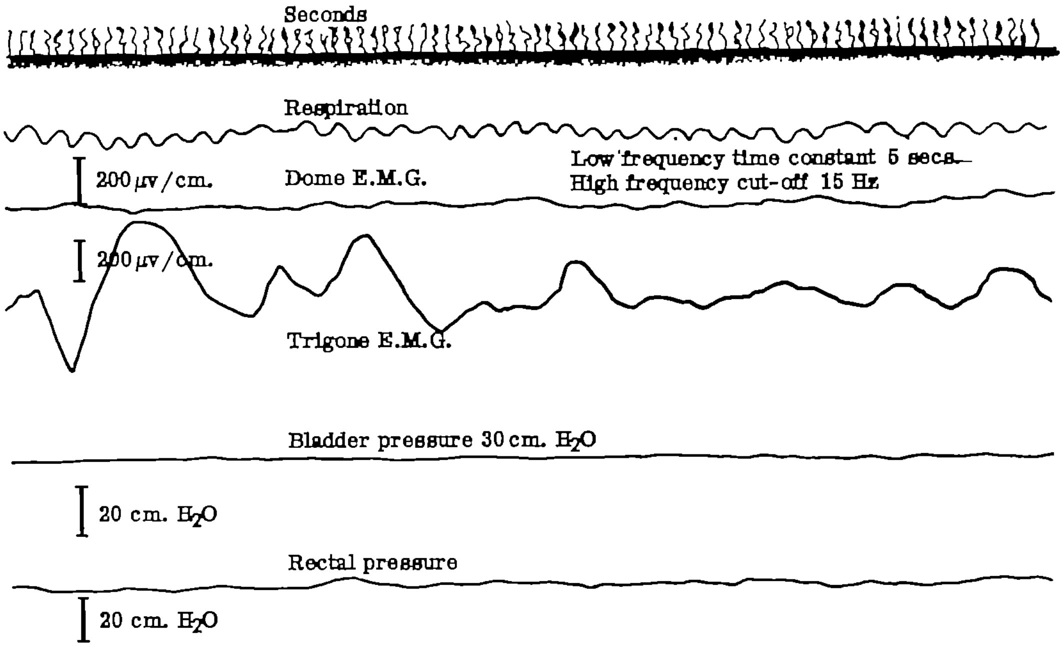

Fig. 3. Dome and trigone detrusor E.M.G.

correlation in the diagnosis of detrusor dysfunction in 19 of the 27 cases. The amplitude of urethral sphincter E.M.G. was assessed, and compared with the recordings of the urethral pressure profile. We were able to obtain an E.M.G. amplitude consistent with the profile recording in 22 cases, *i.e.* 81 %. In 3 cases we studied the effects of antispasmodic preparations on the low-frequency E.M.G. activity. One patient was given oral flavoxate hydrochloride 200 mg t.d.s., the other 2 were given 50 mg of emepronium bromide by intramuscular injection. There was a diminution of activity in all 3 cases, waves in the frequency range 0·2 to 1 Hz being virtually obliterated (Fig. 4).

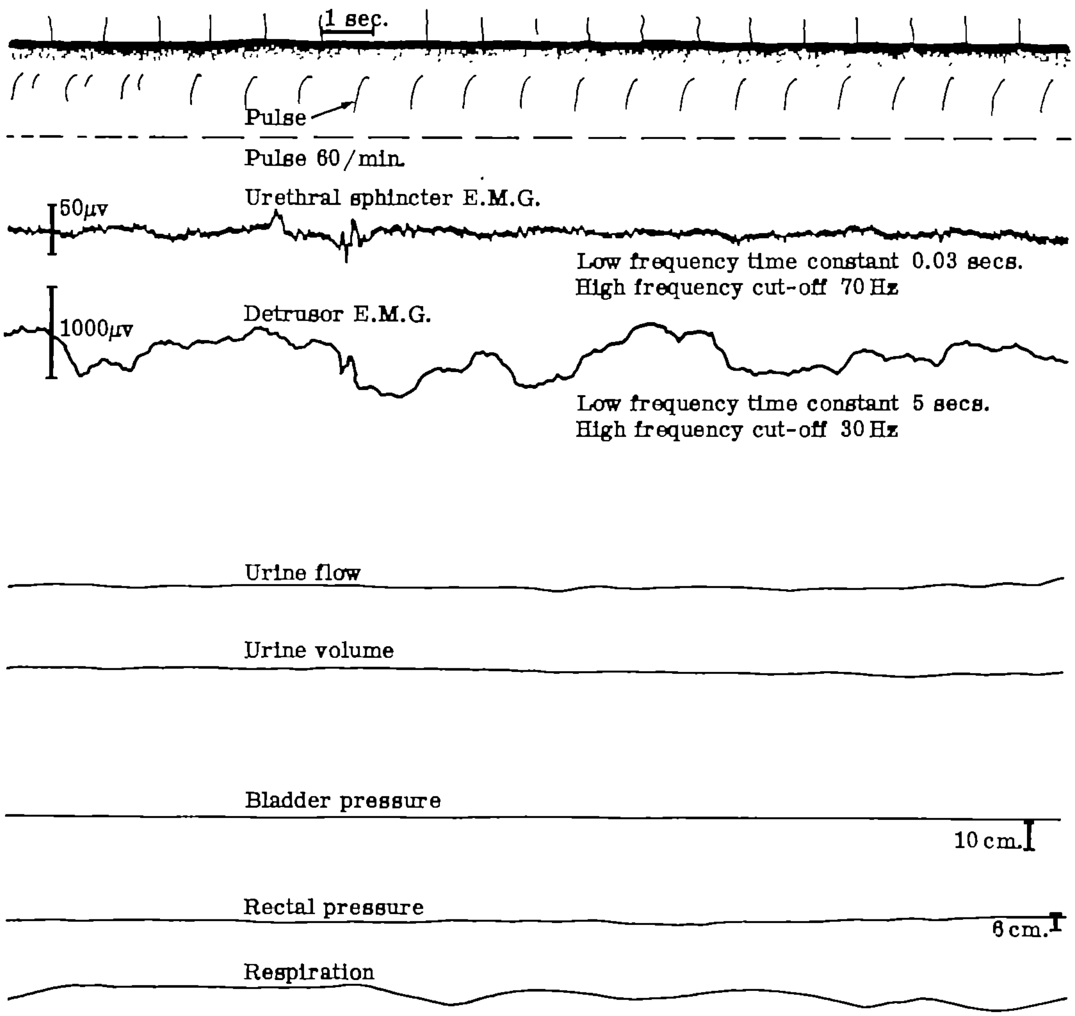

Fig. 4. A, Low frequency detrusor E.M.G. prior to emepronium.

Discussion

Corey *et al.* (1951) and Boyce (1952) obtained regular low-frequency activity from surface electrodes placed against the bladder wall, while Franksson and Petersen (1953) recorded high-frequency activity from needle electrodes placed in the lateral bladder wall via a cystoscope. We feel that the low- and high-frequency activities these workers recorded occur at each end of the frequency spectrum. In our opinion, detrusor E.M.G., particularly the low-frequency component, provides useful diagnostic information.

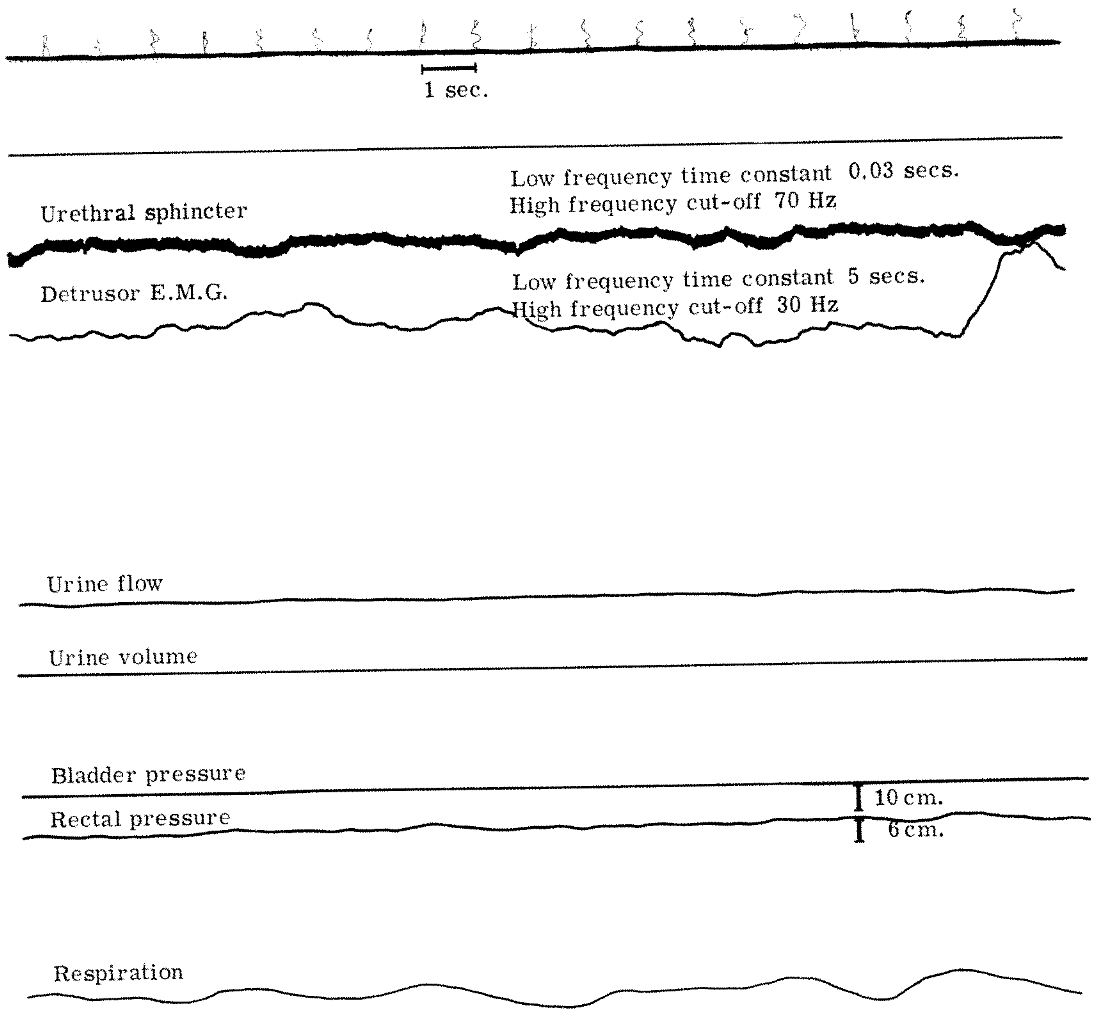

Fig. 4, B, Low frequency detrusor E.M.G. 30 mins after 50 mg. emepronium bromide I.M.

We have found the recordings from the urethral and anal sphincter of great interest. Many workers feel that as the anal and urethral sphincters have a similar innervation, recordings from the anal sphincter which are technically easier to produce give useful information about the function of the urethral sphincter. We question this and can show some differences in the activity of the 2 sphincters. In several patients with pronounced sphincter spasm on the urethral sphincter recording, we have not seen the same activity from the anal sphincter. There is also a marked swing on the anal sphincter produced by respiration. We are able to correlate the amplitude of the urethral sphincter recording with the urethral pressure profile in the majority of cases,

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and feel that recordings from this sphincter give more useful information than recordings from the anal sphincter.

The pressure recordings enable one to diagnose cases of outflow obstruction, and it has been interesting to see the time relationship between changes in intravesical pressure and sphincter relaxation. This is varied within a range of 3 to 13 seconds.

We have found that in cases where the diagnosis is in doubt the recording of so many variables is very worthwhile. In an attempt to gain more quantitative information we are carrying out frequency analysis of both bladder and sphincter activity by means of a digital computer.

Summary

The place of detrusor and sphincter electromyography in the investigation of patients with urodynamic problems is discussed. The low-frequency component of the detrusor E.M.G. and the urethral sphincter recordings are of diagnostic value, and the pressure and flow recordings provide further useful diagnostic information.

It is a pleasure to acknowledge the help of Mr M. Barker and Sister E. Gilbert of the Incontinence Unit, and Sisters Meehan, Rodwell and Prince with the staff of Barrington Ward.

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Discussion

Mr E. P. ARNOLD (*London*):

I was interested to hear your paper but am concerned about the validity of the recordings. My experience confirms how difficult it is to obtain any meaningful electromyographic recordings from the detrusor smooth muscle and to identify them from movement artefact even under ideal experimental conditions in the electrophysiology laboratory.

Typical propagated spike potential can be obtained readily using intracellular electrodes, but elude us in standard extracellular recordings. Because of the irregular arrangement of smooth muscle fibres compared to striated muscle, any one fibre is in surface contact with many other fibres. In addition there are multiple nexus junctions between adjacent cells with low electrical resistance. It may be that the failure to detect electromyographic recordings results from the rapid dissipation of the spike potential across these junctions.

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Vesical Leukoplakia Progressing to Carcinoma

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It is widely accepted that there is a relationship between vesical leukoplakia and vesical neoplasia, but the number of cases of vesical leukoplakia which progress to carcinoma is very small. The first case in this category was reported by Holley and Mellinger (1961), and a similar type of case was reported by Kelalis, Emmett and DeWeerd (1963). Two further cases were reported by us (O'Flynn and Mullaney, 1967) when we reviewed a series of 20 cases of leukoplakia and observed the development of squamous cell carcinoma in 2 patients. Continued surveillance of this group of cases resulted in the observed development of 3 further cases of squamous cell carcinoma. This finding, indicating as it does a possible 25% incidence of carcinoma developing in leukoplakia of the bladder, greatly affects the treatment of this condition. It is also apparent that when a carcinoma does develop in vesical leukoplakia it is extremely malignant, and that early diagnosis is very difficult.

The pathological diagnosis of vesical leukoplakia is confined to those cases showing squamous metaplastic mucosal changes with definite keratinisation, parakeratosis, sometimes with a stratum granulosum, and usually showing the presence of intercellular bridges. The cystoscopic criteria for the diagnosis of this condition have been previously described (O'Flynn and Mullaney, 1967), and in all the cases referred to here the diagnosis has been confirmed by biopsy and pathological examination.

Each case described here was reported on in the previous publication (O'Flynn and Mullaney, 1967), and *the case number quoted here refers back to the assigned number in that study*. The histological material has been re-studied.

Case Reports

H. C. (No. 3). A male, aged 37, was first seen in 1938 and treated by dilatation for a traumatic urethral stricture. Vesical leukoplakia was diagnosed in 1954, but squamous metaplasia of the bladder had been found and confirmed by biopsy in 1950. Subsequent treatment consisted of repeated urethral dilatation, transurethral resection of prostate (done for vesical outlet obstruction which developed during the period of observation), and repeated cystoscopy for diagnostic and therapeutic reasons. 26 cystoscopies and repeated biopsies were carried out over a period of more than 18 years. Carcinoma was first suspected on cystoscopic examination on 23rd April 1969, but cystoscopic biopsy of the suspected area then, and again 7 months later, were both negative. Another biopsy on 8th December 1969 showed the presence of a squamous cell carcinoma. Bilateral ureterocolic anastomosis was carried out as the patient's age and general condition did not permit a total cystectomy. Palliative deep X-ray therapy was given. The patient died on 9th December 1970 in another hospital, without clinical evidence of neoplastic spread. No postmortem was done.

Pathological Commentary. This mucosa was of the flat, keratinising type (see Fig. 3, 1967 paper). Biopsies in 1968 showed a typical leukoplakic picture (Fig. 1), and biopsy a year later demonstrated the onset of squamous cell carcinomatous changes (Fig. 2).

A. E. (No. 7). A male, aged 23, was first seen in 1949 with a 5-year history of intermittent frequency, dysuria and haematuria. Leukoplakia was diagnosed by biopsy. Subsequent treatment included repeated cystoscopic diathermy, silver nitrate instillations and temporary suprapubic cystostomy. In all, 46 cystoscopic examinations for diagnostic and therapeutic reasons were done. Carcinoma was first suspected on 8th December 1970. An area on the left side of the trigone described as "nodular" was biopsied and showed an "invasive undifferentiated carcinoma, probably

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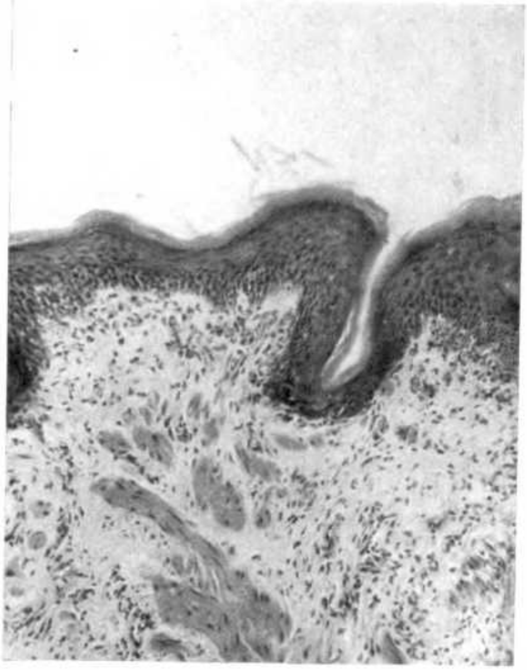

Fig. 1

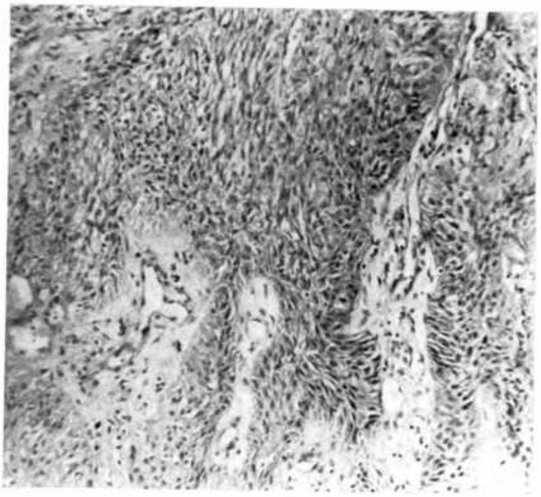

Fig. 2

Fig. 1. Leukoplakia, Group I, with prominent stratum granulosum and keratinisation. (Haematoxylin and eosin. × 125.)

Fig. 2. Infiltrating squamous cell carcinoma. (Haematoxylin and eosin. × 125.)

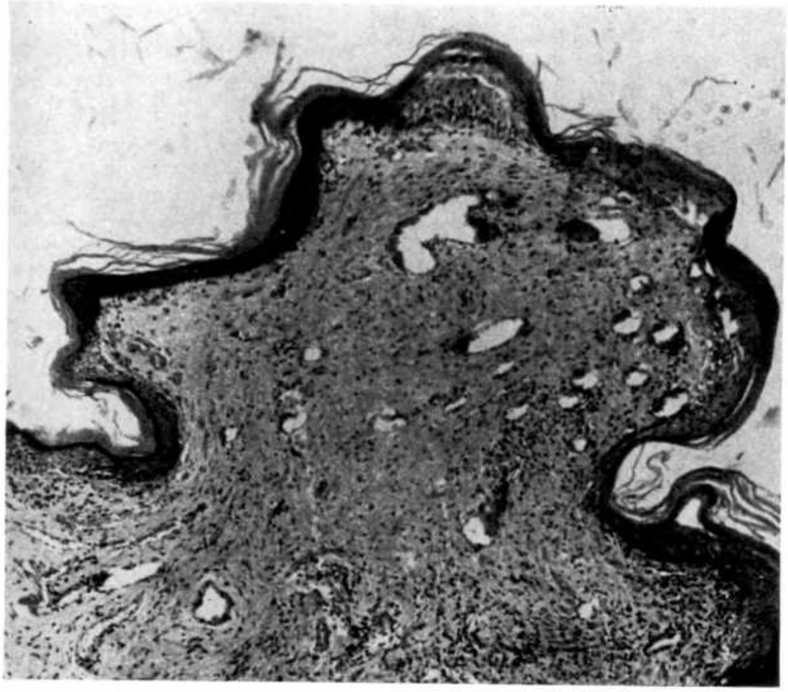

Fig. 3. Leukoplakia, Group I. Laminated keratinisation, prominent stratum granulosum, thin layer of prickle cells. (Haematoxylin and eosin. × 125.)

squamous". Bilateral ureterocolic anastomosis with total cystectomy was done, but the patient died on 9th June 1971. At autopsy the relevant findings were the presence of carcinomatosis peritoneii, hydroureter, hydronephrosis with focal acute and chronic pyelonephritis. No evidence of leukoplakia of the ureter or renal pelvis was found.

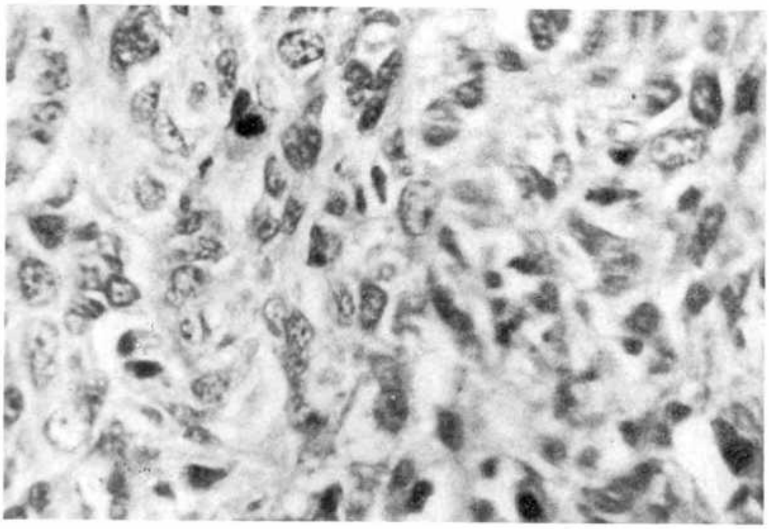

Fig. 4. Anaplastic carcinoma with mitoses. (Haematoxylin and eosin. × 560.)

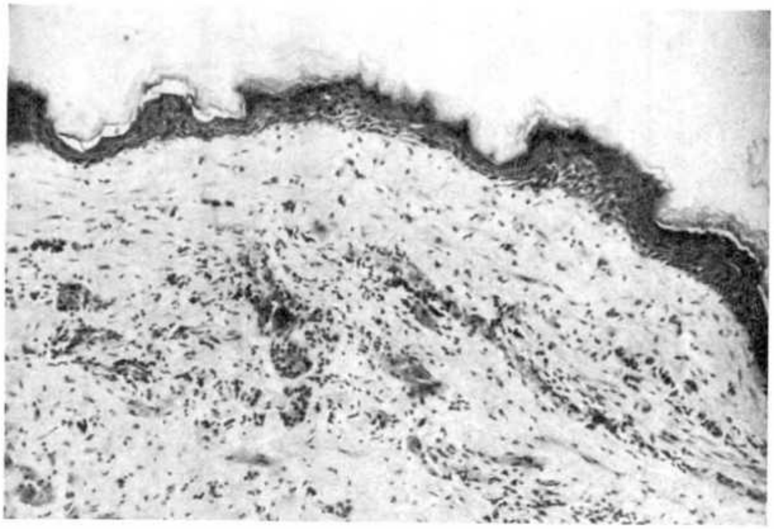

Fig. 5. Leukoplakia, Group I, with marked sub-epithelial oedema. (Haematoxylin and eosin. × 125.)

Pathological Commentary. In 1950 the vesical tissue showed a thin, atrophic epithelium with fairly well-marked keratinisation (Fig. 3). The cystectomy specimen 21 years later measured 5 × 6 × 4 cm with considerable mucosal thickening and a roughened papillary fundal mucosa. Microscopically, there was a diffusely infiltrating, poorly differentiated carcinoma (Fig. 4) extending into muscle. The non-neoplastic vesical mucosa showed a thin epithelium of leukoplakic type with focal stratum granulosum formation and oedematous sub-epithelial tissue. Parakeratosis was absent.

J. M. (No. 16). A male, aged 26, was first seen in 1942 with a complaint of frequency and dysuria and was found to have urinary infection associated with bilateral pyeloureterectasis, horseshoe kidney and reflux. Leukoplakia was first diagnosed in 1960 and this was treated symptomatically, but he developed a contracted bladder and multiple recurrent perineal fistulae, for which bilateral cutaneous ureterostomy was done on 28th June 1967. Up to that time 6 cystoscopies had been done and no evidence of neoplasm was noted. Because of a complaint of haematuria a cystoscopy was done on 19th March 1971 and a doubtful area showing leukoplakia was biopsied and reported as squamous cell carcinoma. Total cystectomy was performed on 31st March 1971. The patient died in 1972, having developed intestinal obstruction associated with extensive intra-abdominal spread of the original neoplasm.

Pathological Commentary. The vesical mucosa in 1966 (Fig. 5) was keratinised, without parakeratosis, but had a stratum granulosum and a thin linear prickle cell zone. The sub-epithelial tissue was oedematous and contained mixed inflammatory cells. The cystectomy specimen (1971) showed a friable tumour on the posterior wall. (No other information was available on the gross material.) Microscopically, there was a squamous cell carcinoma with early cell nest formation (Fig. 6) and superficial extension.

Of the original series, 10 cases have died—5 of these with known cancer as described. Of the other deaths, 1 case, K. D. (No. 6), died suddenly—she had been known to be hypertensive; M. W. (No. 20), had advanced cardio-respiratory disease and developed a faecal fistula after ureterocolic transplantation: no definite evidence of carcinoma was seen; A. B. (No. 2), died elsewhere of "uraemia"; 2 further cases, J. K. (No. 13) and M. M. (No. 15), died of unknown causes. Five further cases were lost to follow-up, but at least 3 of these were known to be alive and well a number of years after the diagnosis was established. The 5 available living cases are still under observation at our department.

M. D. (No. 8), first diagnosed in 1957, has developed a markedly contracted bladder. Biopsy (1972) showed no evidence of carcinoma, but diversion and probable cystectomy are indicated because of severe symptoms and it is hoped to carry this out soon.

R. K. (No. 11), first diagnosed in 1962 when he had a transurethral resection of a small area of leukoplakia at the internal urinary orifice, has shown no evidence of any recurrence. He was alive and well in 1973.

J. L. (No. 14), first diagnosed in 1957, had a ureterocolic anastomosis done in 1960. He has remained well up to 1972 with no symptoms referable to the urinary tract.

J. G. (No. 19), first diagnosed in 1965, had a thin type of leukoplakia with no evidence of any hypertrophic changes, and repeated biopsies carried out up to 1972 showed no evidence of malignancy. She has occasional attacks of urinary infection but otherwise remains well.

A. C. (No. 4), first diagnosed in 1958, had a bilateral ureterocolic anastomosis carried out in 1967 and, because of the findings of this study, had a "prophylactic" cystectomy in 1972 and is of special interest. The removed bladder was somewhat shrunken in size and on being opened presented a curious shining, silvery, skin-like vesical mucosa. Macroscopic examination showed a specimen of bladder measuring approximately 7 × 7 × 5 cm which, opened, had a thick white mucosa and the attached ureters measuring 3·5 cm long, one of them being slightly dilated. Microscopic examination showed diffuse typical vesical leukoplakia with marked keratinisation. There was epithelial oedema present, but no atypia was found. Chronic interstitial fibrosis with scattered inflammatory cells and endarteritis obliterans were present. The metaplasia appeared to cease at the uretero-vesical junction (Fig. 7), the ureters being lined by transitional epithelium (Fig. 8). Scattered chronic inflammatory cells lay in the sub-epithelial ureteric tissues with oedema and hypertrophy of the muscle. There was virtual absence of stromal chronic inflammation in the metaplastic areas in contrast with the normal transitional epithelial zones showing fairly diffuse chronic inflammatory cell infiltration. No neoplasm was seen.

In the years 1967 to 1972, 3 further cases of leukoplakia have been seen at our department. None of these had any evidence of neoplastic change.

Discussion

As previously suggested (O'Flynn and Mullaney, 1967) there may be 2 types of squamous epithelial change associated with vesical leukoplakia, and histological examination of the biopsy and postmortem material indicated that the cases might be divided into 2 broad groups.

Group I had a heavily keratinised, flat, thin type of epithelium with features resembling lichen

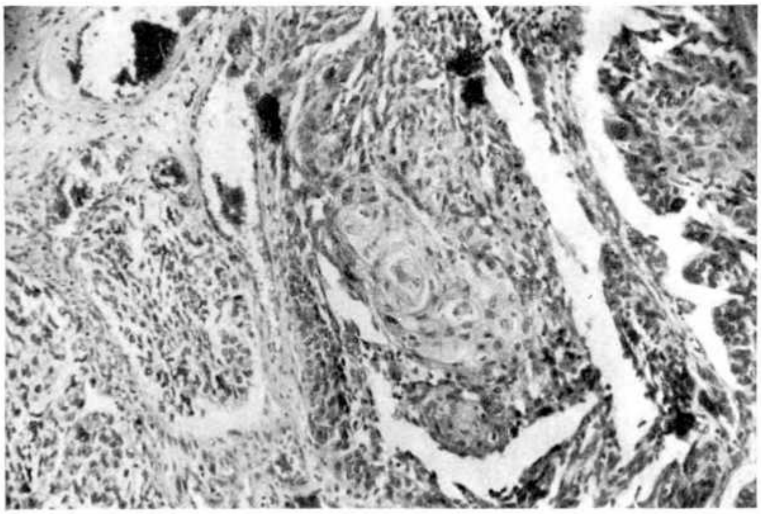

Fig. 6

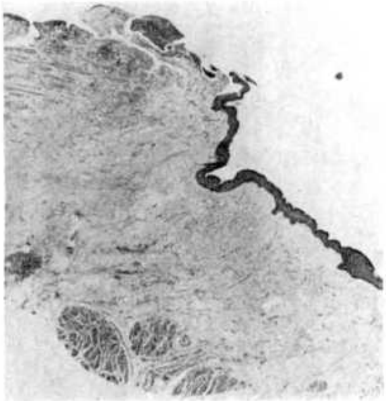

Fig. 7

Fig. 6. Early cell nest formation in squamous cell carcinoma. (Haematoxylin and eosin. × 125.)

Fig. 7. Uretero-vesical junction showing abrupt cessation of leukoplakia. Ureteric mucosa on left. (Haematoxylin and eosin. × 50.)

Fig. 8. Ureteric mucous membrane. (Haematoxylin and eosin. × 125.)

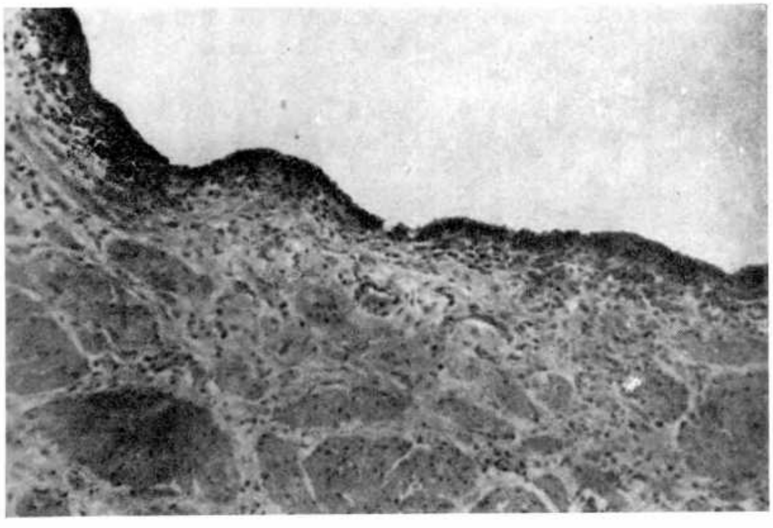

Fig. 8

sclerosis et atrophicus (L.S.A.). Histologically, L.S.A. shows a variable degree of hyperkeratosis, no parakeratosis, a prominent stratum granulosum and a thin acanthotic layer. Oedema of the basal cells is occasionally present and the superficial layer of the sub-epithelial tissues is typically hyalinised, apparently oedematous, with a deep zone of inflammatory cells. L.S.A. has not been described as occurring in the urinary bladder. Seven cases showed this resemblance to L.S.A., and this included 4 of the cases who developed carcinoma. One case (A. C. No. 4) had a prophylactic cystectomy and no neoplasm had developed. Of the remaining 2 cases, 1 (A. B. No. 2) died of "uraemia" elsewhere 6 years after diagnosis; the other (K. D. No. 6) died of hypertension 23 years after diagnosis.

Group II had histological characteristics resembling the features of leukoplakia in sites elsewhere in the body, characterised by hyperkeratosis, irregular hyperplasia of the prickle cell layer with lengthening and abnormal shape of the rete pegs, often showing denticulate processes, hyalinisation of the sub-epithelial zone, absence of elastic tissue and a varying degree of inflammatory cell reaction, but without atypia. 13 cases fitted into this group, only 1 of whom developed carcinoma—(No. 12).

While these 2 groups were broadly distinct, there was some intermingling of features, and in the re-study of the histological material, 1 case (J. M. No. 10) was transferred from Group II to Group I (Fig. 5).

The role of infection in relation to leukoplakia of the bladder is in doubt as all the cases had infection at some time. It raises the possibility that leukoplakia may be primarily a congenital condition, and becomes manifest only when urinary infection develops.

The possibility of assessing the prognosis with regard to the development of carcinoma is obvious, but the series is too small to determine the validity of this and there appears to be no correlation between the cystoscopic and the histological findings.

Wallace (1971), referring to vulval leukoplakia, asserted that it is dangerous to use the term "leukoplakia" only when atypical cells are seen. He also stated that "direct transition from cytologically benign epithelial hyperplasia to invasive carcinoma is quite usual in this situation", *i.e.* the vulva. This view correlates with our finding that it "may be impossible to predict future malignant change by histological examination" (O'Flynn and Mullaney, 1967) in urinary bladder leukoplakia. Toluidine blue was used by Collins, Hanson and Theriot (1966) for the detection of the onset of neoplasia in leukoplakia of the vulva: this might be a possible diagnostic aid in long-standing vesical cases, but has not been tried in this series.

The significance of this study is that there is a very high incidence of squamous cell carcinoma developing in bladders in which leukoplakia has been present for a period of years. All the cases developing carcinoma were long-standing—the original 2 described were 14 years and 5 years—and the later cases showed neoplastic changes at 19 years, 22 years and 11 years after the diagnosis of leukoplakia. All the cases who developed carcinoma were males. Repeated cystoscopic examination gave no early warning of the development of carcinoma and in no case was spread of the disease controlled by cystectomy. As has been shown, 1 case developed carcinoma 4 years after urinary diversion, and it would appear that urinary diversion does not prevent the onset of neoplastic disease. As can be seen from the material presented, there is no certain pathological finding that will indicate whether a given case of vesical leukoplakia will develop neoplastic change or not, but with the evidence of such a high incidence of carcinoma developing in vesical leukoplakia it now seems that the best treatment is total cystectomy.

Summary

Five cases of squamous cell carcinoma of the bladder were observed to occur in a series of 20 cases of vesical leukoplakia.

All the neoplasms which had developed were highly malignant and not amenable to therapy. Total cystectomy should be considered for all cases of vesical leukoplakia.

We wish to thank Mr Victor Lane and Professor Dermot O'B. Hourihane for their co-operation.

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The Suprapubic V-incision

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The classical Pfannenstiel incision was originally designed for gynaecological procedures in which the proximal and distal extent of the exposure is rarely critical. Many urological procedures are however more demanding, and while the distal access can be improved by a midline incision into the lower margin of the rectus sheath, the upward extension of a transverse incision remains compromised by the limitations of the inguinal canal mechanism.

It is perhaps not widely appreciated that a better exposure can be obtained by the simple modification of a V-shaped incision in the anterior rectus sheath (Fig. 1, A and B).

The pyramidalis muscle arises from the front of the pubis, not its crest, and the rectus sheath overlying it is attached to the pubis quite low on the anterior surface. In practice, therefore, the apex of the V-incision is truncated to a 4 to 5 cm horizontal incision just below the upper margin of the pubic symphysis and this is extended steeply upwards and laterally to reach the lateral border of the rectus muscle about the level of the anterior superior iliac spine; it remains entirely within the aponeurotic anterior rectus sheath up to this point, without encroaching upon the lateral musculature.

This procedure seems to reduce the incidence of the development of inguinal herniae resulting from the transverse incision in the male and it also facilitates their synchronous repair when indicated. Like many other surgeons, it is our routine practice to repair any pre-existing inguinal herniae at the time of prostatectomy and under these circumstances we personally prefer a cord-exteriorising Halstead procedure using a continuous monofilament nylon suture to close first the posterior wall of the canal and subsequently the external oblique to form a single effective layer. Any slight tendency to lateral tension in the V closure can be relieved by advancing it slightly on the V-Y principle.

The problems involved in the inguinal area are less important in the female, for whom the horizontal Pfannenstiel incision was designed; partly because the mechanism is less critical in that it is virtually non-conductive, and partly because of the generally wider disposition of the female pelvis.

Retraction of the lower skin margin is simply achieved by suturing it temporarily to the anterior pubic fascia for the duration of the operation by a single midline suture (Fig. 1, C).

The basic suprapubic V-incision naturally affords an improvement of upward exposure without any extension, providing access to the middle third of the ureter above the iliac vessels (Fig. 1, C). It provides good exposure for all lower urinary tract procedures including stones in the lower ureter, total cystectomy with urinary diversion and the supra-iliac psoas bladder hitch procedure for replacement of the lower ureter. For most of these we prefer to use a ring retractor developed with Messrs Down Bros. and Messrs Thackray; this has a range of simple blades, some of which are malleable and all have a matt black finish to reduce light reflection (Fig. 3). The depth

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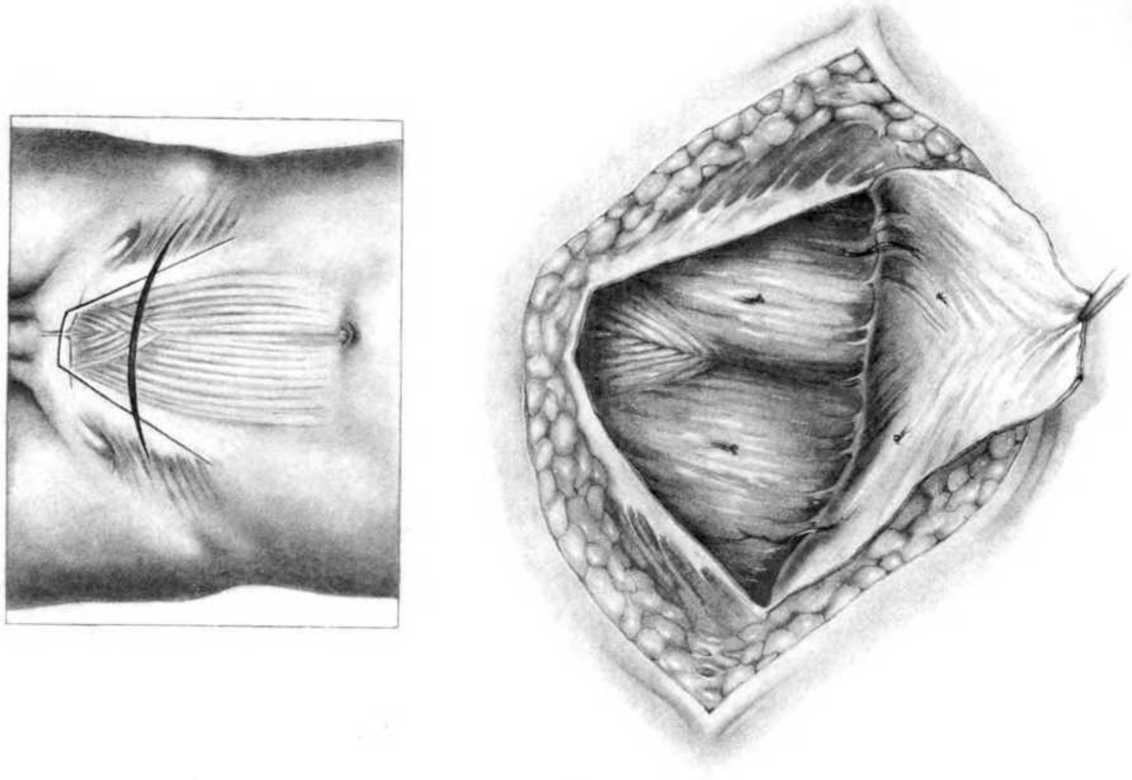
of the lateral blades of the standard Millin prostatectomy retractor compromises its use for the increased lateral exposure provided by the simple V incision because they impinge upon the pelvic brim and iliac vessels; they can be usefully modified by removing their deep extension and increasing the curvature of their inner lip (Fig. 1 C).

If an increased upward exposure is required, a relatively small incision into the abdominal wall muscle lateral to the rectus, in line with the original rectus sheath incision, provides an extraperitoneal approach to the kidney (Fig. 2); this may be useful occasionally for the visual verification of the cystic nature of a renal mass when, for instance, this represents an incidental finding on routine pre-prostatectomy pyelography. Such an exposure can also be useful for the resolution of a problem associated with a complete duplication of an upper urinary tract in which it may be helpful to visualise and palpate a doubtful hemi-renal element before deciding whether to reimplant a refluxing ureter or to proceed with a hemi-nephroureterectomy.



1A 1B

Fig. 1. The suprapubic V-incision.

If a renal procedure is indicated there is an option between a re-approach through the loin or a definitive extension of the V-incision through the lateral abdominal wall musculature to the tip of the 11th rib which provides an exposure for nephro-ureterectomy; this incision can be further extended into a supracostal extension above the 11th rib (Turner-Warwick, 1965) providing an excellent exposure for radical nephro-ureterectomy with pre-mobilisation ligation of the renal vessels (Fig. 3).

In practice it is not usually necessary to divide the rectus muscle itself either for the limited or definitive extension of the suprapubic V-incision and we prefer not to divide it unnecessarily.

Although a low suprapubic V-incision in no way compromises a resection of the pubic bone to improve the exposure of the apex of the prostate, it may not be the best incision for a re-anastomotic supramembranous urethroplasty for urethral strictures following fracture-dislocation injuries, since we feel that the results of this procedure are improved considerably by a synchronous omental pedicle-graft wrap (Turner-Warwick, 1973); this usually involves the definitive mobilisation of the gastro-epiploeic arch from the greater curvature of the stomach up to the splenic pedicle and a xiphisternum-to-pubis midline incision is usually more appropriate for this.

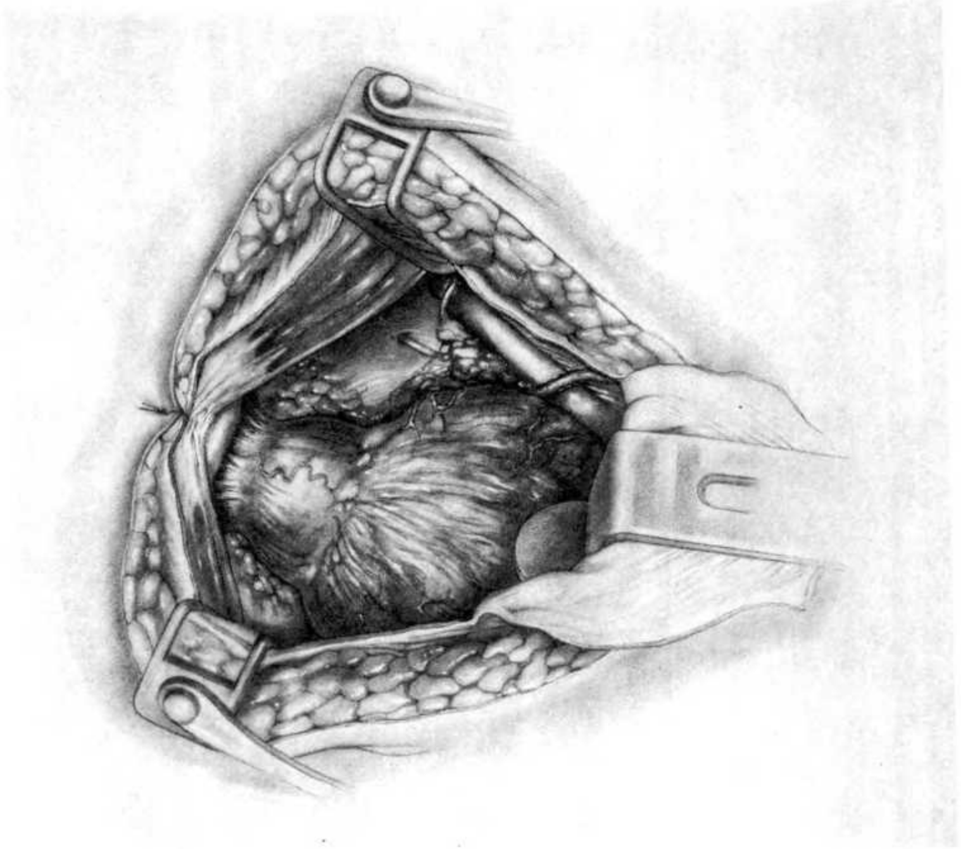


Fig. 1, C

A suprapubic V-incision is, of course, also generally useful for problems outside the urinary tract, especially those relating to the genital tract. In the male we routinely explore an undescended testicle through the appropriate half of the suprapubic skin incision; if simple exploration of the external inguinal area reveals that extensive mobilisation of the testicular vessels is necessary this may be more efficiently carried out trans-abdominally through a V-incision as this has the added advantage that the inguinal canal mechanism remains unmolested. In the event that the testis is found to be in a high position it can be mobilised on the basis of a broad peritoneal pedicle including the local blood supply and that around the vas, but with ligation of the short testicular vessels: in our experience this manoeuvre has been successful in achieving a scrotal positioning of 5 out of 7 high intra-abdominal testicles in post-pubertal patients without further apparent diminution in their size.

In general surgery the V-incision provides a good approach for appendicectomy in the scar-conscious female since the skin incision can be sited below the hair-line; it provides specially good access for the synchronous pelvic laparotomy that is necessary to exclude the diagnostic queries relating to the adnexae and the facility of upward extension is necessary only occasionally to retrieve a retrocaecal appendix.

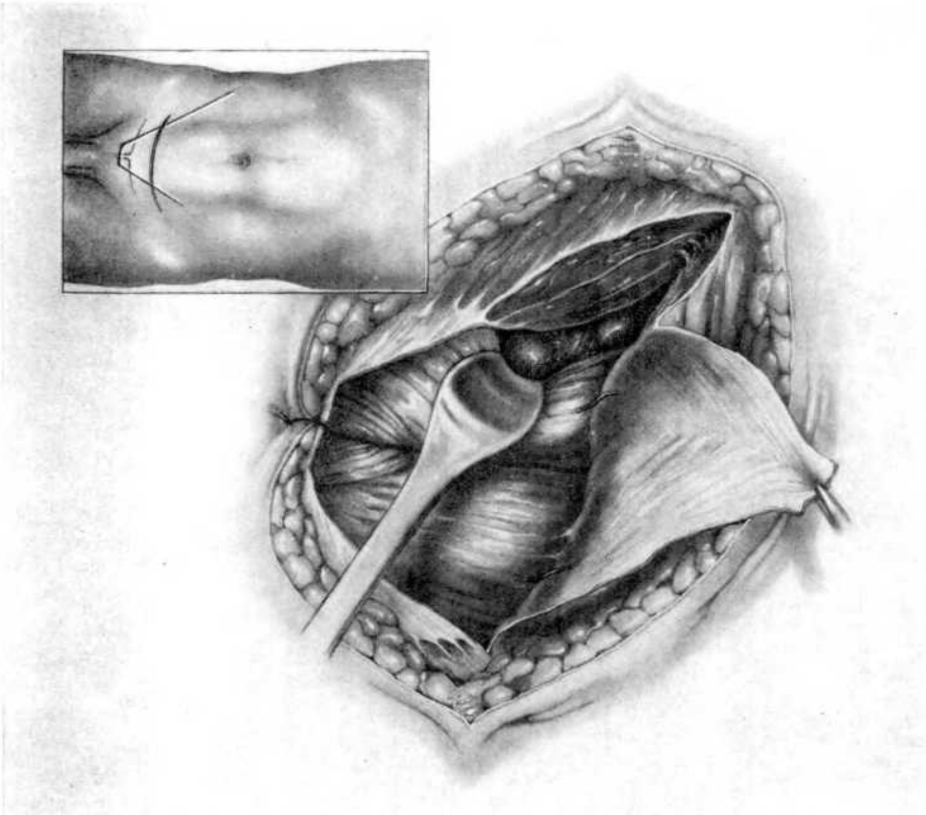


Fig. 2, A and B. Partial extension of the V-incision, lateral to the rectus without dividing it to expose the lower pole of the kidney.

The reliability of the closure and healing of the incision seem to be comparable with that of the Pfannenstiel. We usually use a continuous absorbable suture, interrupted into thirds by head-to-tail ties.

We have used this incision as a routine over a period of years in the Urological Department at the Middlesex Hospital. The incidence of wound infection does not appear to have increased but it is obviously important to avoid a wound haematoma by effective drainage, either laterally to the rectus muscle or through a midline stab incision in the upper flap. We have occasionally seen ischaemic changes in the upper skin margin in elderly patients, but these are rare; it seems important not to separate the subcutaneous tissue from the fascia but to raise the V-flap as a whole and to avoid excessive division of perforating vessels in the elderly. A small area of impaired cutaneous sensation sometimes occurs overlying the flap. The incidence of postoperative inguinal herniae in the male seems to have diminished compared with the horizontal incision; the only ones we have seen have been associated with an indirect sac which was not detected at the time of the initial procedure.

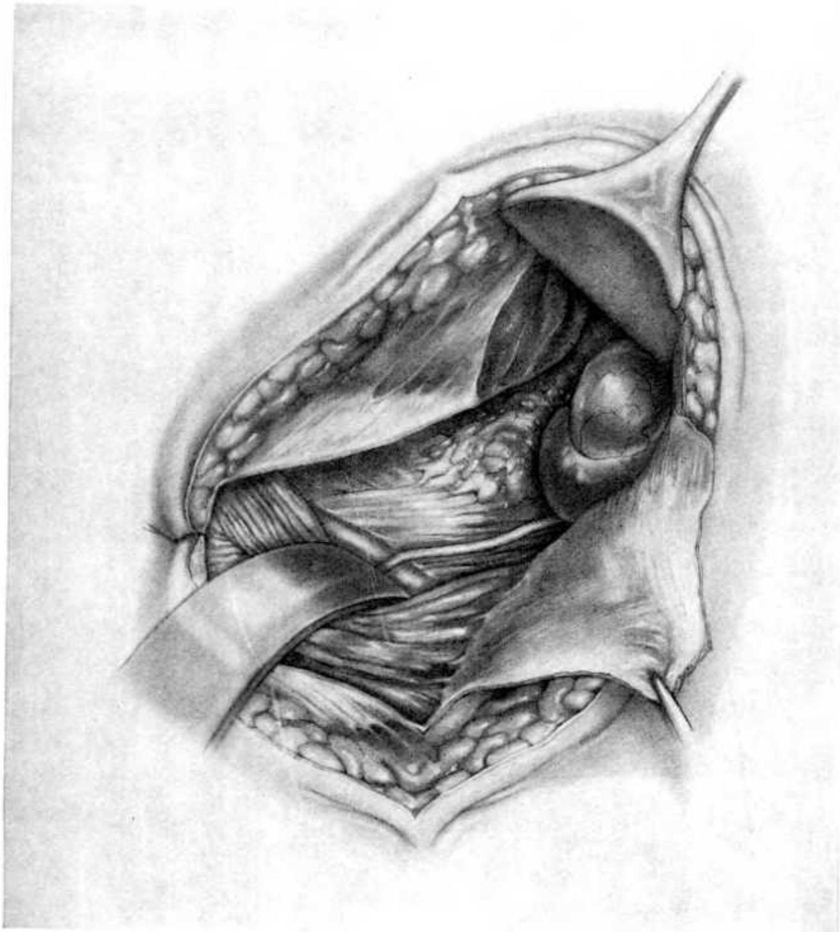


Fig. 2, C

In summary it is often appropriate to use an incision which can be extended without difficulty; the suprapubic V-incision seems to have several advantages over the horizontal Pfannenstiel as an approach to the lower urinary tract and is a considerable alternative to a median incision for many of the more extensive urological procedures.

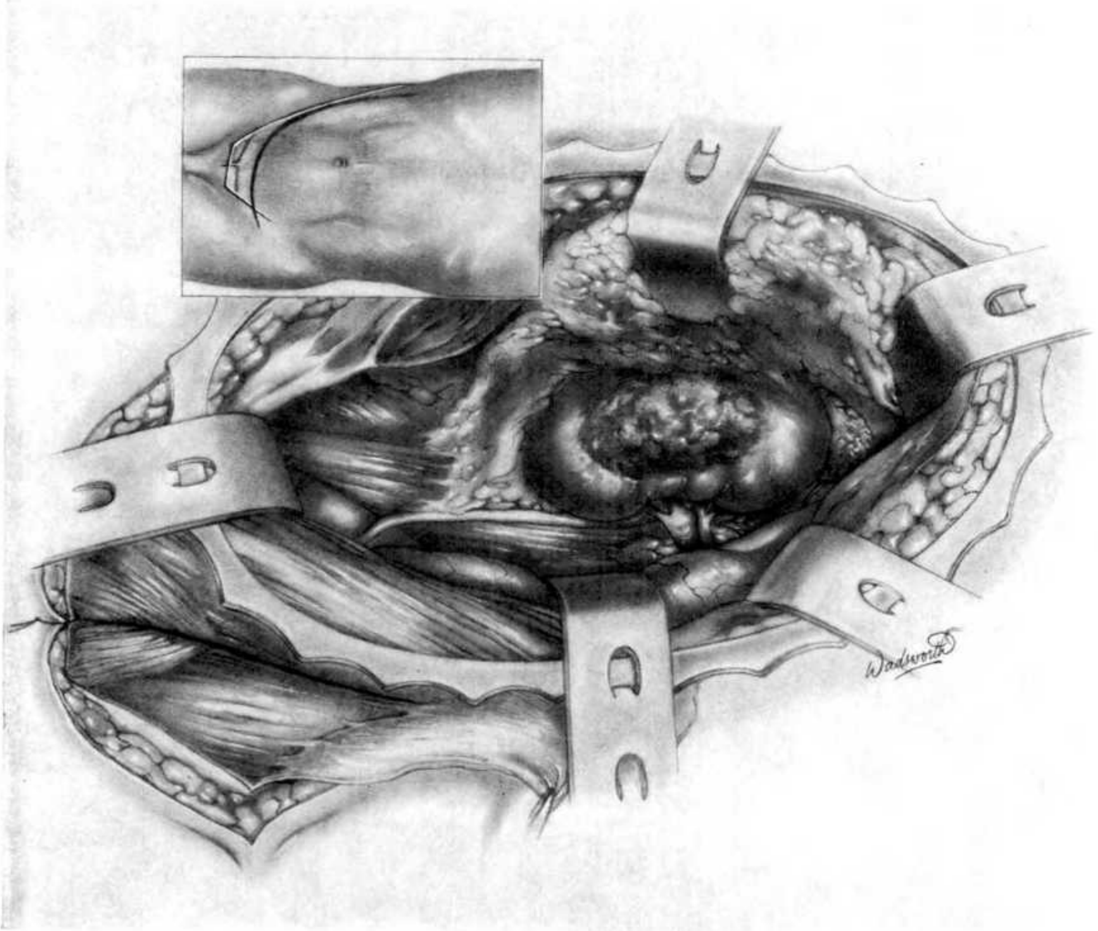


Fig. 3. Definitive extension of the V-incision above the 11th rib for radical nephroureterectomy.

We are most grateful to Miss Freda Wadsworth of the Institute of Urology for the illustrations.

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Anatomical Factors in Prostatitis

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Much has been done in recent years to establish the anatomy of the bladder and its sphincter system and, since it is so intimately related to the sphincters, this has provided a clearer understanding of the anatomy of the prostate gland. This work is associated most with the names of Tanagho and Smith (1966), Gil-Vernet (1968), Hutch (1972) and McNeal (1972). Prior to their contributions, the anatomy of the prostate was confusing—as is the conception of prostatitis at the present time.

This paper seeks to apply some of this anatomy, together with original anatomical observations, to what is known of bacterial prostatitis; also in particular, to relate this anatomy to the aetiology and the pathology of the condition and to the anomalies of the findings in the expressed prostatic secretion (EPS) as this appears to have a direct bearing on surgical treatment when this becomes necessary.

Materials

The observations made follow from a study of a series of cases of lower urinary tract infection in both naval and civilian patients and from a study of a number of normal prostates obtained at postmortem examination. These were serially blocked and studied both grossly and microscopically. Histological material from prostates removed by total prostatectomy for prostatitis has also been used and this material was obtained from the Department of Pathology, the Institute of Urology, London.

Only inflammation of the true prostate as defined by McNeal (1972) is considered. Benign prostatic hyperplasia introduces anatomical and pathological complications which make inflammation in this condition a separate entity; it has therefore been excluded.

Observations

General Anatomy

A personal series of cases of prostatitis shows that the condition is already occurring at the age of 20. Although the age specific incidence appears to increase with age, the condition occurs significantly during the third, fourth and fifth decades (Blacklock, 1969). At this time the gland is formed entirely of the true prostate as described by Hutch (1972) and McNeal (1972). A midsagittal section of the gland of a man aged 22 demonstrates the salient features (Fig. 1).

That part of the true prostate which lies above the level of the verumontanum (V) is separated from the urethra by what McNeal has termed the pre-prostatic sphincter (P), a downward continuation into the urethra of the deep trigone and internal sphincter. Only the lower prostate distal to the verumontanum is directly contiguous with the peri-urethral tissues. Acute inflammation of the true prostate may therefore occur without concomitant inflammatory changes in the prostatic urethra as can be seen in endoscopic photographs (Figs. 2 and 3). In both, the vascular

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pattern of the urothelium is normal and there is no oedema, but in Figure 3 pus can be seen exuding from a duct opening above the verumontanum.

An Anatomical Basis for the Aetiology and Pathological Findings

McNeal (1972) has subdivided the true prostate into a central and peripheral zone on the basis of histological differences in the ducts, the stroma and the epithelium (CZ and PZ, Fig. 1). The central zone of McNeal corresponds with the median lobe of Hutch (1972) except that the central zone surrounds the ejaculatory ducts. The peripheral zone of McNeal corresponds largely with the posterior lobe of Hutch and wraps itself around the posterior three-fourths of the urethral wall.

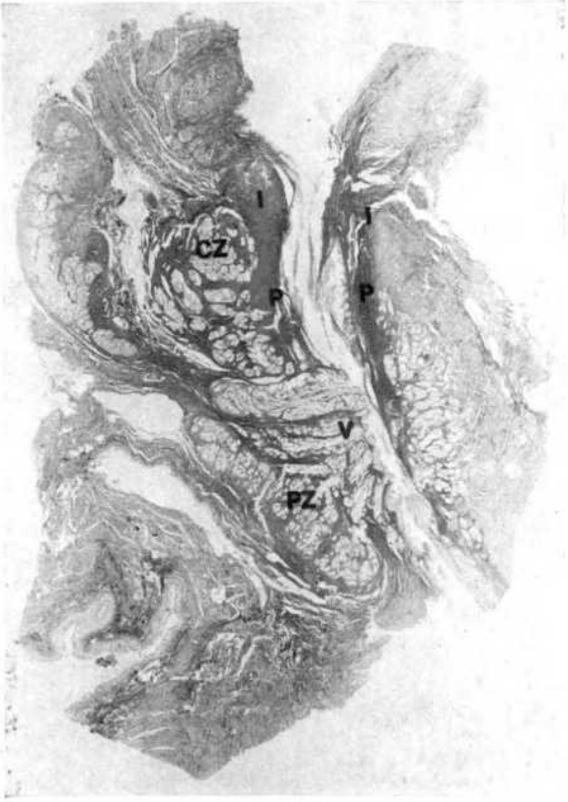


Fig. 1. Mid-sagittal section of prostate gland of man aged 22. V, Verumontanum; I, internal sphincter; P, pre-prostatic sphincter; CZ and PZ, central and peripheral zones of true prostate. Van Gieson. × ½ approximately.

In his study of the pathology of the gland, McNeal (1968) has drawn attention to the markedly greater frequency with which the peripheral zone of the prostate is involved in inflammation. In 40 cases which had histological evidence of prostatitis, the inflammatory change was confined to the central zone in only 2; the peripheral zone was solely affected in 24 and in 14 both the peripheral and central zones were involved although in these the central zone was usually affected in continuity with the inflammation in the peripheral zone suggesting that infection had "spilled over" from the peripheral into the central zone.

The relative distribution of inflammatory lesions between these 2 zones can be accounted for on the grounds of an ascending route of infection and various anatomical factors.

Clinical support for a sexually acquired ascending infection in prostatitis is provided by the finding in a personal series that the disease is more than twice as common in the married as in the single man (Blacklock, 1969). There is additional, more specific, support in the finding of a similar organism in the introitus of the spouse or sexual partner to that found in the expressed prostatic secretion of some patients (Blacklock, 1973; Stamey, 1973). This suggests that micro-organisms ascend the urethra in the early stages of intercourse and are not thereafter ejected at the time of ejaculation. Several anatomical features favour this eventuality.

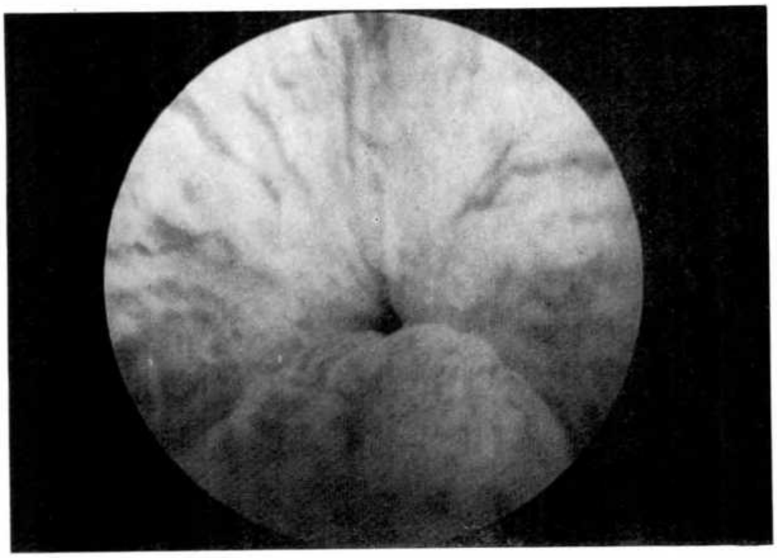


Fig. 2

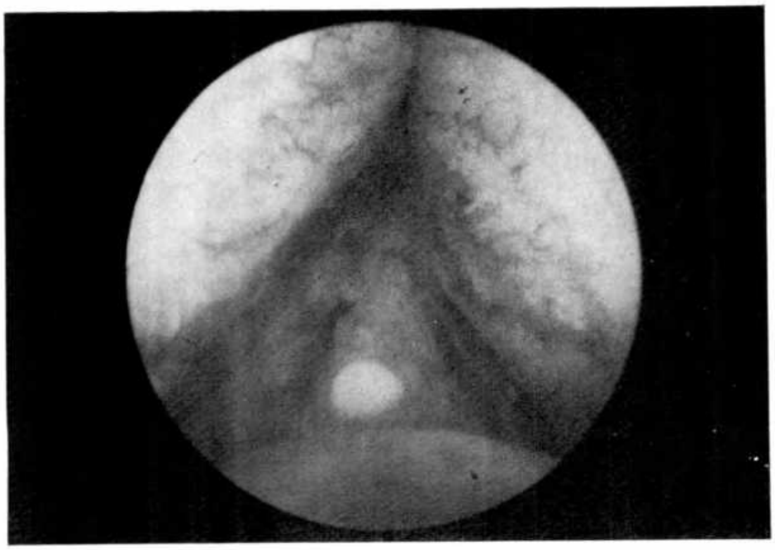


Fig. 3

Figs. 2 and 3. Endoscopic photographs of prostatic urethra in acute prostatitis. There is a normal vascular pattern and no oedema but in Figure 3 pus can be seen in the mouth of a prostatic duct.

In considering these it is necessary to recognise the prostatic urethra as functionally sphincteric above the verumontanum and ejaculatory at and below this (McNeal, 1972); it is also essential to consider that in sexual function three phases are involved:

1. Pre-ejaculatory
2. Intrinsic ejaculatory
3. Extrinsic ejaculatory.

In the pre-ejaculatory phase, the pre-prostatic sphincter (P, Fig. 1) and internal sphincter (I, Fig. 1) are progressively contracted, closing off the prostatic urethra proper from the bladder. McNeal (1972) referred to the fan-shaped downward and anterior direction of the fibres of the pre-prostatic sphincter and a fibrous, and therefore more rigid, lower anterior extremity of this (F, Fig. 4). It is reasonable to deduce that the direction of pull of these muscle fibres is as shown and that in addition to closing the upper part of the prostatic urethra this secondarily increases the size of the lumen of the lower prostatic urethra at a time when the external sphincter (E, Fig. 4) is relaxed, allowing communication between the prostatic urethra proper and the urethra below. Just as these features are maximally favourable for ejaculation, so do they provide maximum opportunity for the ascent of micro-organisms up the urethra and into the lower prostatic urethra at this time. Since the prostatic ducts which open into this part of the urethra are those from the peripheral zone of the gland, micro-organisms will more readily and more frequently enter these than those of the central zone at a higher level.

In the intrinsic ejaculatory phase, the seminal vesicles and ejaculatory ducts eject their contents along the lumen of the prostatic urethra. Simultaneously there is contraction of the intrinsic musculature of the prostate gland as it expels its content into the ejaculate. This might be expected to dislodge any micro-organisms which had already gained access to the prostatic ducts. The histological anatomy of the gland, however, suggests that the central zone (CZ, Fig. 1) is more active in ejaculation than the peripheral zone (PZ). As in the section in Figure 1, the fibromuscular septa are more prominent in the central than in the peripheral zone and suggest that this part of the prostate is more of a functional unit with the ejaculatory ducts and seminal vesicles than the peripheral zone which, with less of an intrinsic musculature, appears to have a less active role. Furthermore, the ducts of the central zone are parallel with the ejaculatory ducts and both sets of ducts are virtually in the line of the lower or true prostatic urethra. Although not well seen in the present section (Fig. 1) which is midline and the utricle is prominent, other sections confirm the original observation of McNeal (1968). This arrangement favours the ejection of the contents of the ejaculatory ducts and of this part of the prostate down the urethra. By contrast, the ducts of the peripheral zone, and especially those from its lower part, enter the urethra at right angles to, and even obliquely against, the direction of flow down the urethra (Figs. 1 and 4). Duct disposition of this kind clearly cannot contribute to the propulsion of fluid down the urethra and an inference of both this and the finer fibromuscular stroma of this part of the gland is that its function in ejaculation is solely to produce turbulence in the stream of ejaculate from the central zone and ejaculatory ducts, in this way ensuring adequate admixture of all 3 constituents of the seminal fluid. An additional implication is that the product of the peripheral zone acini materially differs from that of the central zone and necessitates mixture with the other constituents of the seminal fluid at the time of ejaculation. In consideration of the manner of infection of the gland, turbulence produced in the flow of ejaculate in this part of the urethra is more likely to result in micro-organisms being introduced farther into the ducts of the peripheral zone than their expulsion down the urethra at this time.

In the extrinsic ejaculatory phase, the seminal bolus is propelled down the penile urethra by the contractions successively of the closed loops (Hutch, 1972) of the external sphincter (E, Fig. 4), the bulbo-cavernosus and other striated muscles along the urethra. The spasmodic closure of the upper loops of this sphincter, in occluding the lowermost part of the prostatic urethra, will further favour the introduction of micro-organisms into the ducts of the peripheral zone of the gland.

Apart from infection arising in this way during sexual activity, micro-organisms present within the prostatic urethra may similarly be forced into the gland by a rise in pressure in the prostatic urethra during urination as a result of failure of relaxation of the external sphincter or some lower obstruction. Again, those ducts which open at right angles to or obliquely against the direction of flow will be most vulnerable in this situation, once more exposing the peripheral zone to the brunt of the infection. By contrast, the ducts of the central zone, opening obliquely in the direction of flow, will be forced shut in these circumstances, protecting this part of the gland.

An Anatomical Basis for Diagnostic Anomalies

Much of the confusion which surrounds prostatitis results from the inconsistencies in its clinical manifestation. In the acute condition, even with general toxicity and fever, there may in some cases be scant evidence of infection in the urine and expressed prostatic secretion (EPS). This is even more the case in chronic prostatitis. The presence of an increased number of pus cells in the EPS has been a more consistent finding but the diagnostic reliability of this in the absence of concomitant significant bacteriology has been questioned. The bacteriology of the EPS even in the acute case may be negative and in chronic prostatitis there is considerable inconsistency in this in spite of the most elegant methods of collection and meticulous laboratory techniques (Meares and Stamey, 1972). This has been variously accepted as due to previous antibiotic treatment, bactericidal properties of the prostatic fluid itself, a viral aetiology in the more acute case and an auto-immune basis for the inflammation in the more chronic case.

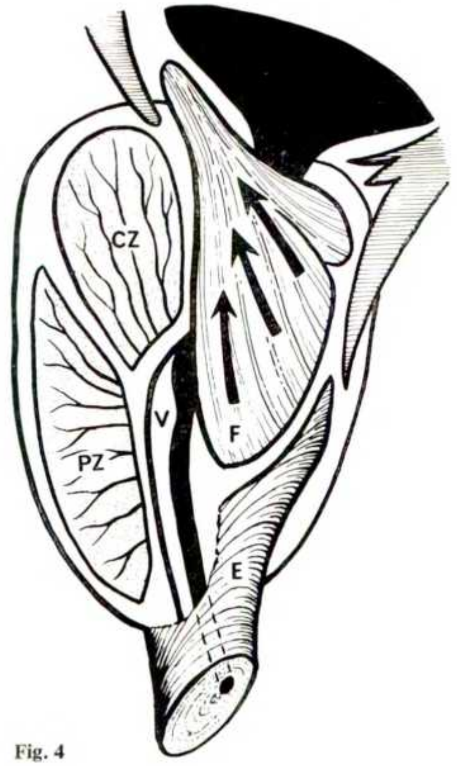


Fig. 4

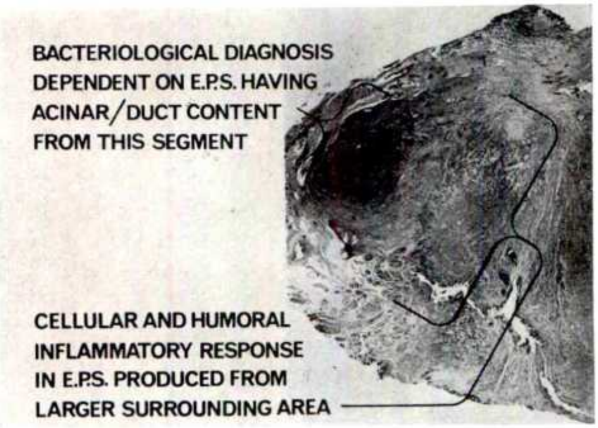


Fig. 5

Fig. 4. Diagrammatic sagittal section of prostatic urethra showing the fan-shaped distribution of the fibres of the preprostatic sphincter and the more fibrous lower extremity of this, F. The closed loops of the striated muscle fibres of the external sphincter, E, are also shown together with the general direction of the ducts of the prostate in their course to the urethra. (Modified from McNeal, 1972.)

Fig. 5. Hemisection of prostate showing a peripheral focus of prostatitis. H & E. $\times \frac{1}{2}$ approximately.

The anomalies of the findings in the EPS in prostatitis and in particular the poor bacteriological correlation are only sustained, however, on the assumption that the EPS contains the products from all parts of the gland. This is almost certainly false. In consideration of the frequently peripheral distribution of infection within the gland, its focal nature and the duct anatomy it is unlikely that the EPS is wholly representative of the gland pathology at any one time. In focal inflammation, which is the characteristic pathology in chronic prostatitis, ducts may be occluded isolating an infected segment at the periphery of the gland in such a way that the contents of the involved acini, including the bacteria, do not appear in the EPS in spite of "adequate" prostatic massage. The parenchyma surrounding such an area, however, may be expected to respond to the focal infection and account for the significant cellular inflammatory response in the EPS in most of these cases (Fig. 5).

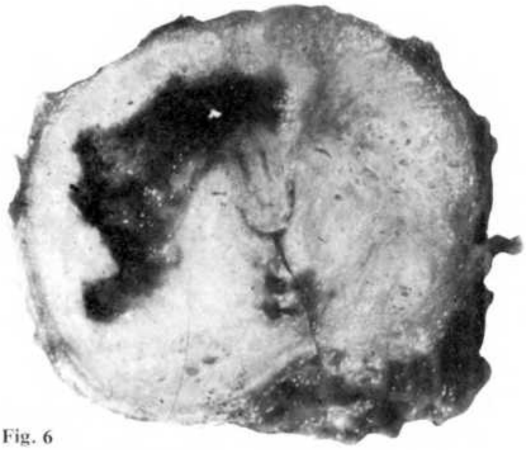
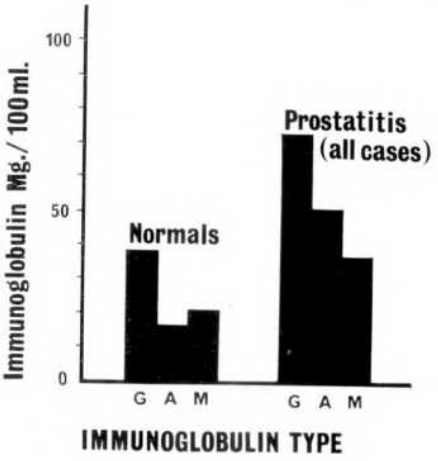


Fig. 6

Fig. 6. Total prostatectomy specimen showing prostatic abscess. (Case of Mr David Wallace.)

Fig. 7. Differential immunoglobulin response in prostatitis. (Gray, Billings and Blacklock, 1973.)



IgG $p = 0{\cdot}025$
IgA $p = 0{\cdot}01$
IgM $p = 0{\cdot}05$

Fig. 7

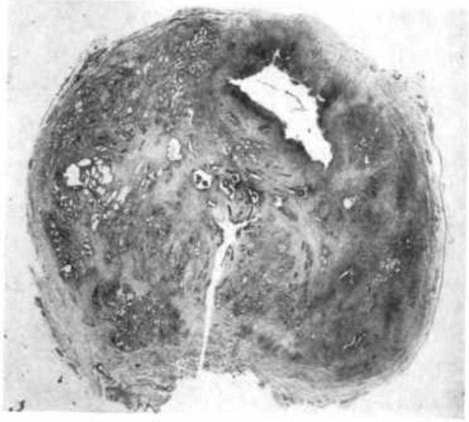


Fig. 8

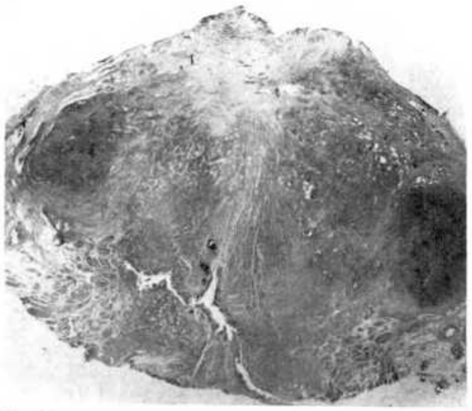


Fig. 9

Figs. 8 and 9. Sections of prostate showing multiple foci of prostatitis, mainly in the periphery of the gland, and a peripheral abscess. H & E. × ½ approximately.

Perhaps the most advanced example of loculated infection is the prostatic abscess (Fig. 6) and it is the experience of some (Dajnani and O'Flynn, 1968; Trapnell and Roberts, 1970) that there may be no indication in the urine of the underlying infection.

Other findings in the EPS in inflammation have been a significant immuno-globulin response (Gray, Billings and Blacklock, 1973; Fig. 7) and a characteristic rise in the pH from the normal of 6·5 to a pH of between 7 and 8, dependent on the severity of inflammation (Blacklock and Beavis, 1973); the nature of this pH response is not known but is under investigation at the present time. These latter phenomena being of a humoral and therefore more general nature have been found to be related more consistently to the cellular inflammatory response of the EPS than the bacteriology which is dependent on the expression of secretion from the infected segments of the gland. The association of a cellular inflammatory response in the EPS and a raised immuno-globulin content, especially immuno-globulin A with its specific indication of parenchymal response, is of particular significance.

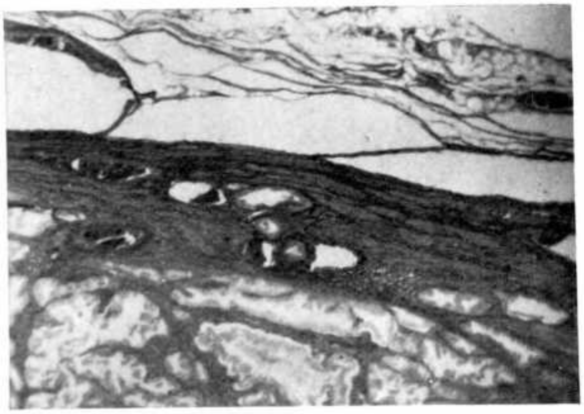


Fig. 10. Section through fibro-muscular capsule on posterior aspect of true prostate at the level of the verumontanum. Van Gieson. × 30.

The Anatomy applied to Surgical Treatment

Most cases of acute inflammation respond satisfactorily to an adequate course of chemotherapy and there is no requirement for surgical treatment unless abscess formation supervenes.

In chronic prostatitis which is characteristically focal, the response to antibiotic treatment is much less satisfactory. In a number of these, symptoms become increasingly troublesome and continuous antibacterial chemotherapy may be required to avoid relapse. In these, both the anomalies of the characteristics of the EPS and the tendency to relapse on cessation of an antibiotic suggest deficient drainage of the products of infection from a loculus in the substance of the gland (Figs. 8 and 9). The continuation of chemotherapy to the exclusion of supplementary measures in such circumstances must offend fundamental surgical principles. The basis of effective treatment at this stage is considered to be either the removal of the focal infection or at least the promotion of adequate drainage of the products of inflammation. Both the nature of the pathology and the pathological anatomy support treatment by transurethral resection in these instances. Although total prostatectomy offers the greatest certainty of complete eradication of the condition the risk of complications limits its acceptability in a benign disease.

The frequency with which prostatitis involves the peripheral zone of the gland indicates the likelihood of resection having to be directed at that part of the urethra overlying it. This may involve resection into prostatic tissue at the level of or just below the verumontanum which is technically both difficult and dangerous. Again, with the frequency of peripheral zone involvement, resection will often have to extend out as far as the so-called true capsule of the prostate which at this level is a tenuous fibromuscular layer (Hunter, 1968) and, as in the section shown (Fig. 10) is barely 1 mm in thickness. Control of the resection by a finger in the rectum is therefore essential and this may additionally define indurated parts of the prostate against the sheath of the resectoscope which are most likely to be foci of chronic inflammation. Both the pathology and the anatomy, which often show multiple, peripheral foci of infection, support a tentative approach to resection in this condition and a number of resections may be necessary before all loculi of prostatitis are removed.

Summary

The intrinsic anatomy of the prostate and the sphincter mechanism of the urethra allows more objective consideration of the aetiology of prostatitis and its pathology.

The pathological anatomy provides a further reason for the anomalies in the characteristics of the EPS and the difficulty of cure in some cases.

It furthermore provides support for a transurethral approach to surgical cure in the cases which advance to this stage.

I wish to acknowledge the considerable technical assistance of Surgeon-Lieutenant K. Bouskill and Mr K. Williamson of the Department of Pathology, Royal Naval Hospital, Haslar. I also wish to thank Chief Petty Officer J. Richards of the Department of Medical Illustration, Mr L. Williams of the Department of Photography and Mrs Bernice Harby for their help.

I acknowledge with thanks the loan of the pathological material used for Figures 5, 6 and 8 from the Department of Pathology, The Institute of Urology, London.

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Chronic Prostatitis—An Australian View

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In clinical practice, it is unusual to obtain convincing evidence that the symptoms and signs which support a diagnosis of so-called "chronic prostatitis" derive from infection with organisms of accepted pathogenicity. The common occurrence of so-called commensal organisms in this common condition does not justify dismissal of the possibility that such organisms may be pathogenic in certain patients. It is possible that the precise organisms responsible for the prostatitis may be retained within the gland and may not be recovered by ordinary methods of sampling of urine and prostatic secretion.

The purpose of this paper is to report the results of an investigation into some clinical and microbiological aspects of chronic prostatitis. It was hoped to find evidence for possible pathogenicity of common organisms which are generally referred to as commensals and evidence for the retention of pathogenic organisms within the prostate gland but recovered by vigorous prostatic massage after wide instrumental overstretch of the prostatic urethra.

Materials and Methods

Observations were made of the leucocyte content and the bacterial population of the prostatic urethra in 57 male patients with clinical signs or symptoms of non-acute prostatic inflammation and in 15 control subjects without clinical suggestion of prostatic disease.

The patients ranged in age from 20 to 72 years with a predominant grouping in the third, fourth and fifth decades of life and with the majority of patients being less than 60 years of age. They presented with the common symptom-complex of some frequency of micturition with urethral discomfort, varying hesitancy and difficulty with micturition and itinerant somewhat weird pains. On clinical examination the prostate was found to be normal or enlarged, soft, boggy, small, firm or hard.

The first 10 of the 57 patients were subjected to very detailed study with the collection of a urethral swab and then initial, mid-stream and terminal samples of urine before prostatic massage for the recovery of prostatic fluid. With forced oral fluids enough urine re-accumulated in 1 hour for a further post-massage segmented urine sampling to be obtained. In the remaining 47 patients and in the control subjects observations were made upon prostatic fluid and initial urine samples obtained before and after prostatic massage.

In each of a select group of 40 patients an attempt was made to improve the prostatic drainage by a forceful overstretch of the prostatic urethra by rotation of a Hindeman bougie about its long axis in the urethra but with the curved end of the bougie lying in the prostatic portion. This rotation was followed by forceful massage of the prostate against the bougie. Blood cultures were taken before and after this procedure which usually provided several millilitres of prostatic fluid for bacteriological study.

Results

In the small group of 10 patients selected for more detailed study it was found impossible to obtain prostatic fluid from 1 patient and in another the fluid was sterile. In the remaining

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8 patients *Staphylococcus albus* was the commonest organism in association with *Streptococcus faecalis*, *Streptococcus viridans* and diphtheroids in various combinations but none of the specimens grew recognised pathogenic organisms. Viable counts of organisms recovered from the segmented urine samples showed that the mid-stream urine was clinically sterile in all but 1 patient (Fig. 1). The pre-massage terminal urine sometimes gave higher counts than the initial urine but in most instances they were either similar or lower. With one exception, the organisms were cultured from the prostatic fluid but viable counts were not applicable to these specimens because of wide variation in size of inoculum. No significant rise was detected in the bacterial counts of the same organisms as the result of prostatic massage.

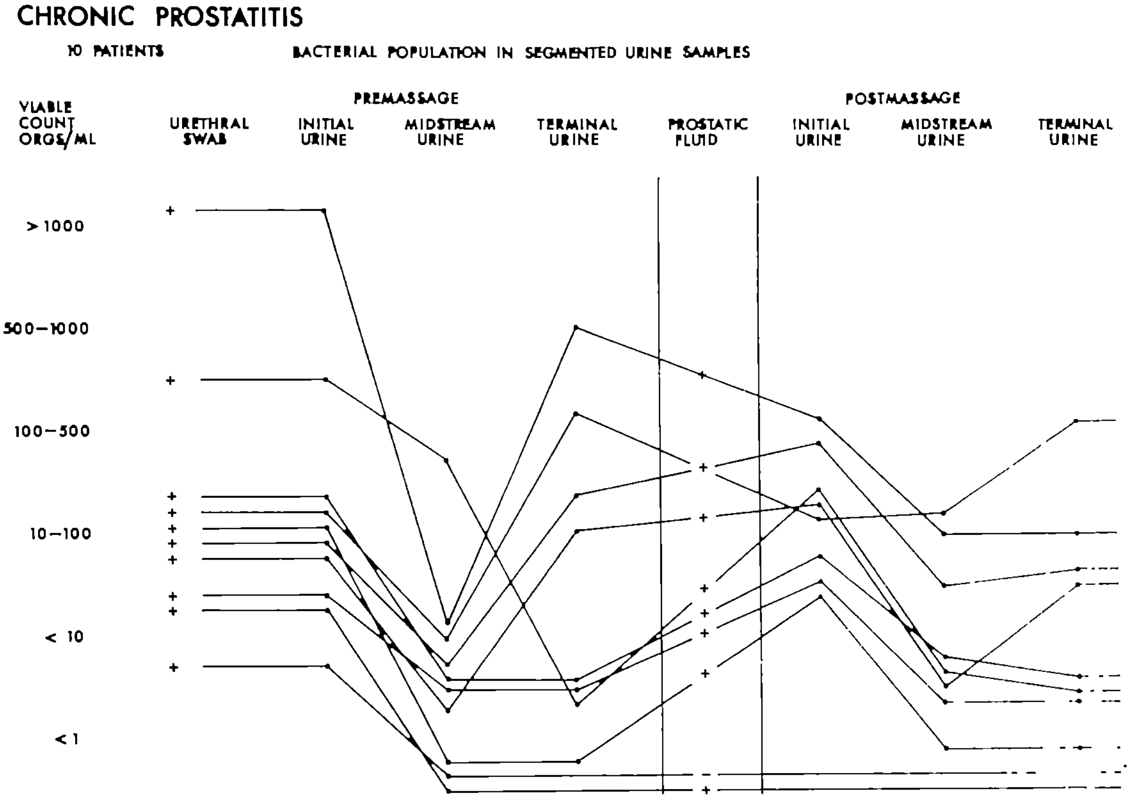

Fig. 1. Viable counts of organisms in segmented urine samples from 10 patients with chronic prostatitis.

In the small series of 10 patients, quite high pus cell counts were obtained in 7 of 8 specimens of prostatic fluid suitable for examination. Counting of the pus cells in the separate segmented urine samples indicated that the count of pus cells which might derive from the prostate could be accurately recorded from the initial urine sample after prostatic massage.

A comparison of pus cell content and viable count of organisms in initial urine samples before and after prostatic massage is shown for both patient and control groups in Figure 2. The leucocyte count in the initial urine samples before prostatic massage was usually less than 10 per ml in both the patient and control subjects. A shift to more than 50 cells per ml was produced in 12 patients and 2 control subjects by prostatic massage. The initial urine samples before and after massage were sterile in 9 patients and 2 control subjects. In the remainder of the series the distribution of organisms was almost identical between the clinical and control groups. *Staphylococcus* *albus* was the commonest organism in both patient and controls (54% and 50%) with *Streptococcus faecalis* (20% and 25%), *Streptococcus viridans* (8% and 15%) and *E. coli* (11% and 10%) occurring less frequently in combined or pure culture. In the control subjects, viable counts in excess of 100 organisms per ml were found in only 1 specimen from any control subject. In both patients and controls, the majority of the viable counts were less than 100 organisms per ml and

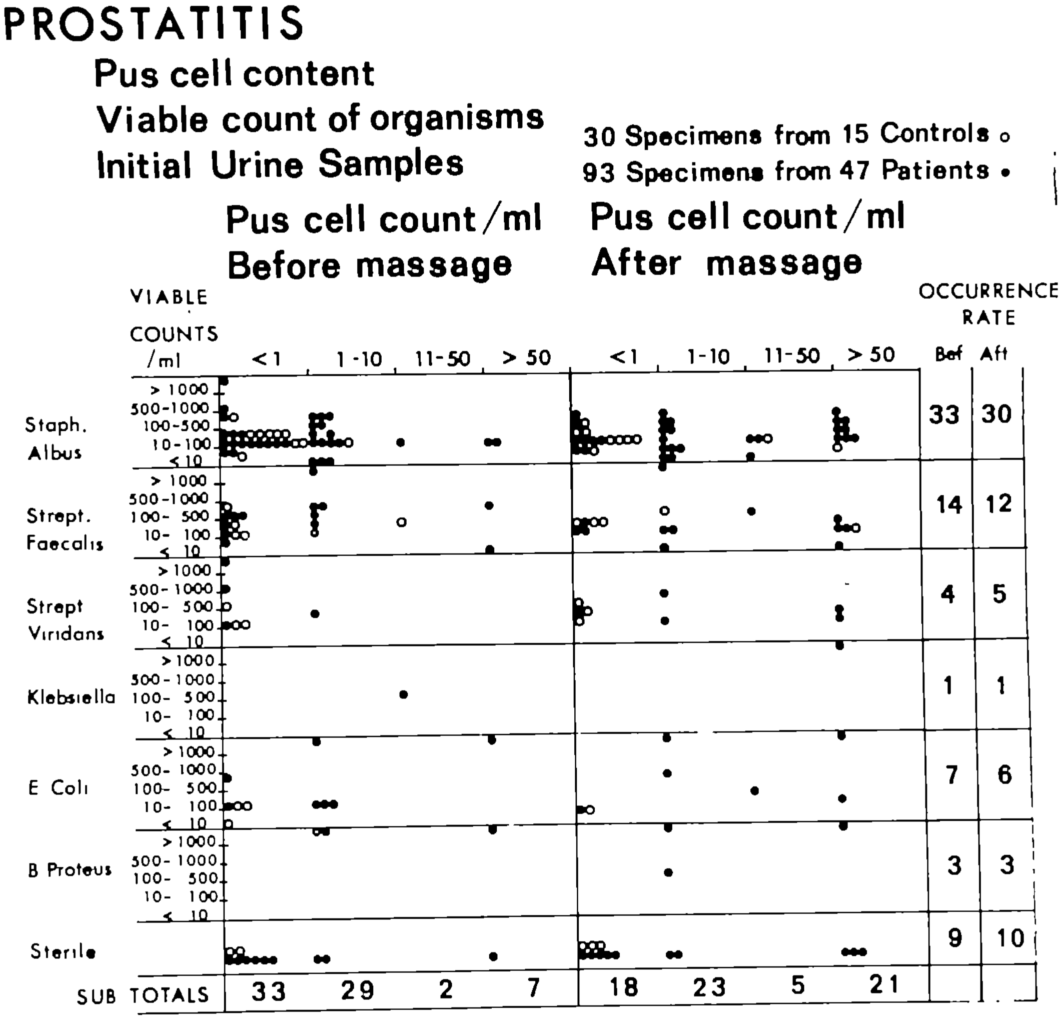

Fig. 2. Relationship between pus cell content and viable count of organisms in initial urine samples before and after prostatic massage in 15 control subjects and 47 patients with chronic prostatitis. (The subtotals and occurrence rates refer to the specimens from patients and exclude the controls.)

prostatic massage did not change the incidence of organisms of different types in the initial urine. Any marked change in the viable count of organisms as the result of prostatic massage was only occasionally noted. Pus cells which were thought to derive from the prostate as the result of massage were not associated with any particular organisms and did not correlate with viable counts which ranged from less than 10 organisms per ml to more than 1,000 per ml.

The pattern of insignificant difference of occurrence rate of organisms in the initial urines before and after prostatic massage was found in each of the different species of organisms. Sterility of initial urine samples was not changed by prostatic massage and more sterile specimens were obtained from the patients than from the control subjects.

Specific drug therapy appropriate to the sensitivities of *Staphylococcus albus* was given to a group of 11 patients and the bacteriological findings of further specimens of initial urine were subsequently reviewed. In only 1 of these 11 patients did the urine sample become sterile but in this select group there was generally a reduction in count of the organisms after drug therapy.

66% of the specimens of prostatic secretion obtained from the 40 patients subjected to urethral overstretch and massage were sterile and this incidence was uniform through those patients who had cultured organisms from their preoperative initial urine samples and was not influenced by the administration of antibacterial drug therapy before urethral instrumentation and prostatic overstretch. When the initial urine specimens were infected before and after urethral instumentation it was usually with the same organisms but in 3 instances the organisms changed as a result of instrumentation and with the emergence of *E. coli*, coliforms and *Streptococcus faecalis*. *Staphylococcus albus* was notoriously absent from the change in urethral flora.

In a great majority of patients treated by this overstretch of the prostatic urethra with gross massage under anaesthesia there has been diminution in the size of the prostate and a return to more normal and perhaps more firm consistency. It is possible that the procedure breaks down the granulation tissue which can be seen to line the posterior urethra on either side of the verumontanum, to allow for better drainage of the inner zone of epithelial glands.

Conclusions

These studies have failed to define any bacterial population in the posterior urethra which is specific to patients with so-called chronic prostatitis. No evidence has been obtained that common commensal organisms such as *Staphylococcus albus*, *Streptococcus faecalis* and *Streptococcus viridans* are pathogenic in prostatitis. Retention of pathogenic organisms within the prostate has not been implicated as a source of recurrence or relapse of clinical prostatitis in this series. The basis for clinical improvement after chemotherapy, antibiosis or urethral instrumentation remains obscure.

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Discussion

MR TURNER-WARWICK

Both transurethral resection and dissection prostatectomy have been advocated as methods of treating "chronic prostatitis" and we can accept that the results of these are sometimes satisfactory—but it is important to analyse the effect of these procedures rather than accept the premise that it is important to perform an extensive resection in order to eradicate hypothetically infective crypts.

"Chronic prostatitis" is a many-faced condition. The prostate may prove to be purulent, infected, inflamed, calculous, immuno-active, hypersensitive or even quite normal.

It is important to appreciate the symptomatology "chronic prostatitis" can be precisely imitated by that of bladder neck obstruction; this form naturally responds magically to resolution of the outflow obstruction which can be effectively achieved by the relatively simple and efficient procedure of endoscopic bladder-neck incision (Turner-Warwick *et al.*, 1973).

In view of the fact that obstructive "chronic prostatitis" is by far the easiest type to treat, it is always worthwhile checking the voiding flow objectively. It is open to question what proportion of the patients who respond to extensive transurethral loop resection do as a result of the incidental resolution of simple bladder neck obstruction.

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A Reconsideration of the Biology of Carcinoma of the Prostate

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In the 15 months from February 1972 we have studied 67 consecutive cases presenting to us as carcinoma of the prostate. 19 of these patients were our old patients, already under treatment, 39 patients were new cases and 9 patients had been treated elsewhere and referred to us for further treatment.

Our policy is to exclude any patient where histological or cytological proof is lacking. In this we failed to substantiate the diagnosis in 3 patients—1 being a granuloma of the prostate and 2 being transitional cell carcinoma of prostatic ducts. In this respect, we note that the treatment of adenocarcinoma of the prostate is commonplace without laboratory proof of the diagnosis (South Metropolitan Cancer Registry, 1972). In this paper we show that such an attitude is indefensible, knowing the morbidity of orthodox treatment.

Table I

Presenting Symptoms and Signs of 67 Patients

Prostatism	25
Acute retention	14
Bone pain of pathological fracture	13
Haematuria	7
Palpable lymph nodes	3
Renal failure	2
Paraplegia	2
Pleural effusion	1

Table II

Diagnosis Established

Retropubic prostatectomy	14
Transurethral resection of prostate	35
"Trucut" needle biopsy	17
"Frantzen" needle biopsy	3
Bone biopsy	3
Cytology after massage	2
Open biopsy	2

Presentation of Patients

Table I shows the common presentation of our patients. Classical prostatic symptoms predominate including acute retention in 20% of these patients, but secondary deposits causing pain or fracture occurred in 25% of these patients. Haematuria occurred in 12%, including 2 patients thought to have carcinoma of the bladder, but confirmed as adenocarcinoma of the prostate, while this excludes 2 patients thought to have carcinoma of the prostate and found to have transitional cell carcinoma of prostatic ducts.

Three patients presented in uraemia with lymph node involvement around the renal pedicles, but with normal ureters, while a further 5 patients were uraemic from obstructed ureters at vesical levels.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

Table II shows the diagnostic methods used. These figures are not mutually exclusive. We frequently use needle biopsy and transurethral resection to make the diagnosis.

It seemed to us that carcinoma of the prostate is a generalised disease. To substantiate this we studied bone surveys by radiology and total body scans by isotope methods. Table III shows that there were many patients who entered the study with no information on metastatic disease, or who later were terminal or too frail for detailed investigation. While almost half of our patients had bone metastases at the start of the study, nearly two-thirds had bone metastases at the conclusion of the study.

To enquire further on the extent of the disease we studied lymphangiograms (Table IV). At the start of the study, we had no information on lymphatic involvement in our patients, but on more detailed study we found that 60% of all our patients had lymph node involvement. This figure is probably far higher for 18 of 30 successive lymphangiograms show lymph node involvement.

Eight patients had lymph node involvement with no evidence of bone disease. We confirm the findings of Aubrey and Peeling (1973) that treatment of carcinoma of the prostate did not seem to affect the insidious course of metastases in bone. This was in contradistinction to lymph node involvement where oestrogen treatment showed improvement in 3 patients.

Knowing the recent re-appraisals of oestrogen therapy we have studied the lipoprotein profile in some of our patients. Initially we had no such information on most patients (Table V). But once treatment with oestrogens started or orchidectomy was performed we found that an abnormal lipoprotein profile was 3 times more common than a normal level in the patients who were studied. This consisted in consistently raised plasma levels of cholesterol, triglycerides and pre-lipoproteins. While we have no actuarial figures on similar people without carcinoma of the prostate, we noted that 4 patients were normal before treatment but became abnormal after treatment: of these 4 patients 2 were treated with stilboestrol at 1 mg t.d.s. and the other 2 patients were following orchidectomy. On a further 11 patients there was no pretreatment data on lipoproteins but 7 had abnormal levels after stilboestrol 1 mg t.d.s. and 4 patients had abnormal levels after orchidectomy.

In our therapeutic protocol we treat localised prostatic disease by external irradiation but it is rare for us to find such localised disease. If there is metastatic disease *de novo* or if localised disease becomes metastatic disease we use stilboestrol 1 mg t.d.s. and a diuretic each morning. We monitor the effect of therapy by serial measurements of plasma testosterone. If the plasma testosterone level progressively rises or bone metastases are concurrently painful we perform bilateral orchidectomy.

Arising from this protocol, we found that fluid retention was commonplace. We have had no further problems on this side since starting routine diuretics—preferably bendrofluazide K 2·5 mg o.m.

However, we have encountered 5 episodes of venous thromboses. All 5 patients were receiving stilboestrol at low dosage. Two of these patients had abnormal lipoprotein profiles. More important were 2 other patients with pulmonary embolism, 1 following low dose stilboestrol and 1 following orchidectomy. Both had abnormal lipoprotein profiles as described.

We have been concerned by the frequent findings of anaemia in our patients. 50% of our patients presented with haemoglobin levels of less than 12·0 G% (Table VI). This is a sinister finding as it is usually associated with bone or lymph node metastases. These anaemias fell into 3 groups, namely iron undersaturation, folate deficiency and B_{12} deficiency.

We had 10 examples of iron undersaturation (Table VII). All had normal B_{12} levels and serum folate levels and all 10 had bone metastases.

We have information on serum folate levels on only 18 of our patients (Table VIII). Eight of such patients were folate deficient. Of these, 3 were converted to normal levels with recovery of their anaemia with folic acid treatment. These 3 patients had no bone metastases. The remaining 5 patients failed to improve with folic acid treatment. All 5 had bone metastases.

Table III

Metastatic Bone Disease

On Presentation	
Positive	32
Negative	16
No information	19
	67
On Subsequent Study	
Positive	40
Negative	11
No information	16
	67

Table IV

Lymph Node Involvement

At Presentation	
Positive	12
Negative	3
Equivocal	3
No Information	49
	67
At Subsequent Study	
Positive	18
Negative	5
Improved	3
Equivocal	4
No information	37
	67

Table V

Lipoprotein Profile

At Presentation		
Abnormal	1	
Normal	8	
No information	58	
Post-treatment		
Abnormal	15	1 from abnormal 4 from normal 11 from N.I.
Normal	5	4 from normal 1 from N.I.
No information	47	

Table VI

Anaemia

No information	18		
Hb below 12·0 g	30	26	Bone secondaries Node secondaries
		1	Node secondaries only
		3	No secondaries
Hb normal	19		
Total	67		

Table VII

Iron Saturation below 20%
(10 patients of 18 studied)

All B_{12} normal
All folate normal
All with bone secondaries

Table VIII

Folate depletion
(8 of 18 patients studied)

3 Improved with Folic acid—no bone secondaries
5 Not improved with Folic acid—bone secondaries

Table IX

B_{12} depletion
(8 of 18 patients studied)

3 Improved with B_{12}—Normal folate
Bone secondaries

Of these same 18 patients 8 patients were Vitamin B_{12} deficient (Table IX). Five of these patients had metastatic bone disease with normal serum folate levels. The anaemia improved dramatically in 3 patients. All these patients were receiving oestrogens throughout.

While folate deficiency secondary to oestrogen therapy has been reported (Strieff, 1970) we noted folate deficiency in 3 patients following orchidectomy. Two of these had bone metastases, but 1 did not. Vitamin B_{12} deficiency in association with oestrogen therapy is unusual. Of our 8 patients, 7 were receiving oestrogens and 1 had undergone orchidectomy.

Our final observation concerns 9 of our patients who presented with hydronephrosis. Three of these patients had normal ureters but lymphangiography showed lymph node involvement around the renal pedicles. These patients with hydronephrosis improved after oestrogen therapy.

Summary

Carcinoma of the prostate is a generalised disease in which most patients have metastases at the time of presentation.

Anaemia is a frequent finding usually with evidence of metastatic disease.

Orthodox treatment with oestrogens or orchidectomy have thromboembolic sequelae, which should be preventable.

Some of the anaemias can be corrected.

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The Significance of Antibodies to Sperm in Infertile Men and their Wives

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Previously (Halim and Antoniou, 1973) we studied 2 types of autoantibody to human sperm: the first caused agglutination of sperm, the second was cytotoxic. Agglutination of sperm is a well-known phenomenon. In certain circumstances it can be recognised on a slide, but the agglutination does not necessarily imply that it is caused by antibodies: other substances in seminal plasma can cause agglutination. When caused by antibodies, sperm-agglutination is followed by lysis, in a way strictly analogous to the agglutination and subsequent lysis which occurs after a mismatched blood transfusion.

The second group of antibodies are cytotoxic: they make the sperm heads swell and burst in a manner strictly analogous to the cytotoxic reaction used in typing HLA antigens for tissue transplantation.

The agglutination of sperm is caused by antibodies quite unrelated to the ABO antibodies: we have found that specific antisera for red cells do not agglutinate sperm. Nor are the antibodies which cause the spermo-cytotoxic reaction those which react against lymphocytes with known HLA antigens; none of the spermo-cytotoxic antisera of our patients will react to the panel of lymphocytes with known HLA specificities which are used to characterise HLA antisera at The London Hospital Tissue Immunology Unit.

In our previous studies we have shown that normal fertile men may have up to 3% incidence of agglutinating and 2% of spermotoxic antibodies in their sera, yet despite this, all of them have fathered children. These incidences increased 6 weeks after vasectomy to 10% and 6% respectively, suggesting that trauma or obstruction may be agencies capable of causing autoimmunisation.

The greatest interest lay in our finding that 15% of the husbands and 17% of the wives of 165 infertile couples showed sperm-agglutinating antibodies in their sera. Agglutinins which make sperm clump together could stop them from swimming up the fallopian tube, and would therefore cause infertility. Having found this, we were puzzled as to what we could do about it.

Table

No. of Cases	Agglutination titre before prednisolone	Agglutination titre after 2 weeks prednisolone treatment
7	1 : 32	1 : 4
1	1 : 32	1 : 16
2	1 : 16	1 : 4

We made a series of pilot studies to see if a small dose of steroids (5 mg prednisolone t.d.s.) would alter the agglutinin titre. There was (Table) a significant reduction in the titre of aggluti-

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

nating antibodies. This suggested a useful weapon with which we could weaken the immunological barrier to fertility.

Furthermore, since antibodies are carried in the seminal plasma, we could try to wash them off the sperm, and inject the washed sperms directly into the wife's cervical canal.

Methods and Materials

We used the technique of measuring sperm agglutination described by Kibrick (1952), improved and modified to render it more sensitive (Halim and Antoniou, 1973).

We used the method for detecting and measuring spermatotoxic antibodies described by Hamerlynck (1970). Sperms killed by the cytotoxic reaction were identified in the phase contrast microscope, and death confirmed by noting the uptake of trypan blue.

A husband (10 cases) who showed antibodies was given 5 mg of prednisolone t.d.s. for 2 weeks prior to the estimated date of his wife's next ovulation. On this date a specimen of semen was collected in a sterile polythene container. The sperms were washed with phosphate buffered saline at pH 7·2, centrifuged at 300 r.p.m. for 30 minutes, resuspended in 1 ml of phosphate buffered saline, and then injected through a number 12 Intracath into the wife's cervical canal. This was done 3 times in each cycle, to bracket as far as possible the date of ovulation predicted by the temperature chart.

A wife (16 cases) who had antibodies in her serum was given 5 mg of prednisolone t.d.s. for 2 weeks prior to her expected dates of ovulation. Her husband's semen was not washed, but was centrifuged for 30 minutes at room temperature at 500 r.p.m.; the supernatant was withdrawn, leaving a 1 ml concentrated residue which was injected as before through an Intracath into her cervical canal, her vagina having been first washed out with 1% sodium bicarbonate at room temperature.

Results

11 pregnancies have been achieved in couples, one or other of whom showed serum antibodies to sperm. One wife miscarried at the 3rd month, but conceived successfully the next time.

To date there have been 7 live births. All followed normal labour: all the babies are normal and are doing well. There are 5 boys and 2 girls.

Discussion

It can be argued that we might have achieved just as many pregnancies if we had left out the cortisone and merely used centrifuged sperms without washing off the seminal plasma. This seems unlikely, since 34 of the couples we have treated had undergone AIH elsewhere before being referred here, and all had been treated at several clinics in the past. Nevertheless, strict caution is necessary in accepting these results, for our experience is small, and our efforts to overcome the immunological barrier had been empirical and clumsy.

But even with these crude techniques, it has been possible to achieve pregnancy in a significant number of cases. With increasing experience we hope further to refine and streamline our technique.

We are glad to acknowledge the advice and assistance of Dr Hilliard Festenstein.

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A Classification and Quantitative Histological Study of Abnormal Ureters in Children

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If the physiology of the ureter is not fully understood its pathology is even less so, and every radiologist and paediatrician knows of children who have had grossly dilated tortuous ureters which on later examination have been normal in size and have apparently functioned normally. How a dilated ureter functions at all is difficult to comprehend.

We have failed to find any detailed study of the quantitative histology of abnormal ureters in children, or indeed any satisfactory classification of ureters for study. Material from among the renal tract abnormalities dealt with by this department has therefore been surveyed and an attempt made to classify the gross abnormalities in the ureter and to relate them to structure.

Materials and Methods

50 abnormal renal tracts held in the department were examined. From these all material was discarded where the ureters were incomplete or had been the site of operative treatment. 78 ureters remained from children ranging in age from 36 weeks' gestation to 5 years.

In this study we have not considered the state of the kidney and have excluded, with the exception of 1 double ureter specimen, cases of abnormalities of ureter entry into the bladder and where there was an apparent congenital stenotic lesion of the lower ureter, as well as children with the so-called "Prune Belly" or "Triad" Syndrome. We are therefore concerned with the apparently embryologically normal ureters and with what are almost certainly secondary changes in the ureters.

The material was treated by the methods described in our previous study of normal ureters (Gill and Emery, 1974) After measuring the length of the extravesical ureter from the pelvi-ureteric junction to the bladder, the ureters were cut into 1-cm lengths and the lumen diameter at each measured by insertion of stainless-steel probes. The intravesical ureter length and diameter were also measured by insertion of probes. The amount of muscle and connective tissue and the relative number of muscle nuclei in transverse sections of ureter were estimated simultaneously by a Point Counting technique using a Swift Automatic Point Counter.

Classification of Ureters

The proposed classification (Fig. 1) is as follows:

Class A (19 ureters). Apparently normal ureters which in the cadaveric and fixed state have a slightly variable lumen diameter, but the largest not exceeding double the average diameter. The ureter wall is not thickened.

Class B (22 ureters). Ureters of normal length which appear to have walls of normal thickness but show areas of increased luminal diameter outside the range of Class A.

Class C (14 ureters). These have a rigid form with relatively little tortuosity and an almost uniformly increased luminal diameter and are occasionally referred to as "lead-pipe" ureters. There is often some thickening of the surrounding connective tissue.

Classes D and E. Represent ureters with increased length, diameter and tortuosity. In Class D (18 ureters) there is great thickening of the wall which is usually uniform throughout the whole length, whereas in Class E (5 ureters) the wall is thin and often transparent.

All ureters could be placed with reasonable ease into 1 of the 5 classes on naked-eye examination.

As our previous study had shown that the quantitative structure of the ureter varied least at the region of the pelvic brim, we present here the measurements from this area and also from a point a third of the distance from the kidney to the bladder.

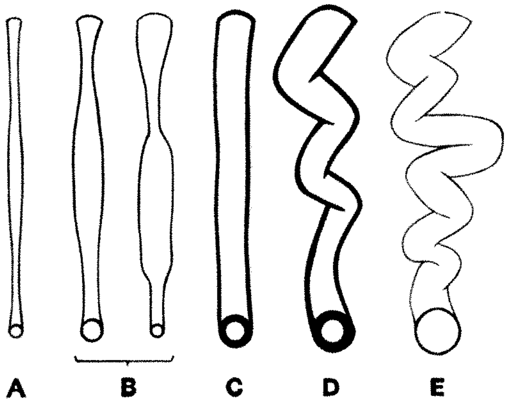

Fig. 1. Showing in diagrammatic form the classification of ureters as applied in the present study.

Muscle

The variable amount of muscle in the ureter is illustrated in Figure 2 which shows projection tracings of ureters from 3 children of the same age at the same magnification. Note the distribution of the muscle in the normal ureter and how study of individual segments of the perimeter would give a false impression of the total musculature. Note also that in the grossly dilated Class E ureter (2) that the thickness of the muscle at any point of the ureter wall is at least that of the normal ureter 1. In ureter 3 when there is gross muscular hypertrophy, the larger bands of muscle tend to be on the outside and the smaller ones nearer the epithelium.

The distribution of the total muscle area in transverse sections of the 5 classes of ureters related to age, together with the mean normal curve, is shown in Figure 3. All the ureters of Class A show muscle areas within the normal range. Class B ureters demonstrate muscle areas within the normal range or slightly increased. In Class D the largest muscle areas were recorded but they do not appear to be age related, whereas in the Classes C and E ureters there is a tendency to an increase in muscle with increasing age. In none of the ureters examined is there evidence of reduction in the amount of muscle.

Muscle Hyperplasia and Hypertrophy

In order to assess hypertrophy and/or hyperplasia a muscle nuclei count was also carried out. The results are shown in Figure 4, where the mean of normal ureters is also indicated. All ureters in Classes A and B fall within the normal range but Classes C, D and E show considerable

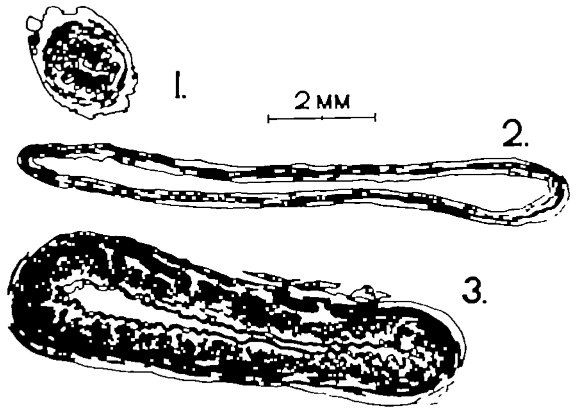

Fig. 2. Photograph of tracings of ureters from children of the same age and at the same magnification: (1) is from a normal ureter Class A, (2) and (3) from abnormal ureters Classes E and C. The muscle is shown as solid black.

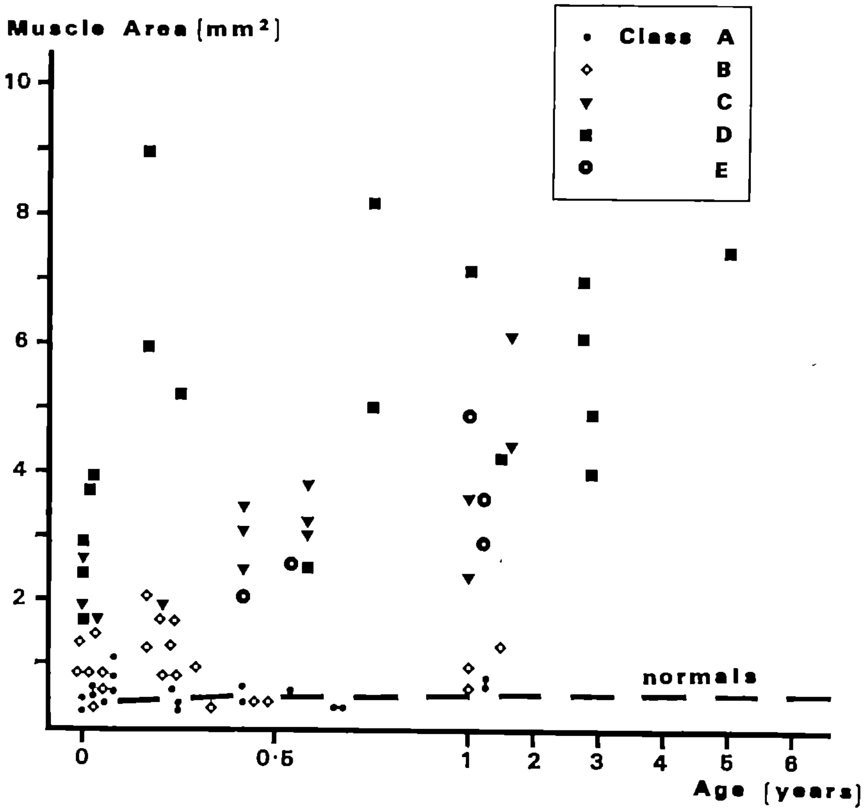

Fig. 3. Figure showing the amount of muscle in complete cross-sections of the ureters related to postnatal age. The mean of the normal range is shown in a dotted line.

variability, and all but two in Class E and one in Class D are above the normal range. If the scatter in Figure 3 is compared with that in Figure 4, it will be seen that when taking muscle area into consideration, the highest 5 readings were all of Class D, whereas when muscle size is considered, only 2 of the Class D ureters are in the first 5, the other 3 belonging to Class C. All Class A ureters appear to be in the normal range. All Class B are in the normal range from the point of view of muscle size, but 45% showed an increase in muscle area, that is—simple hyperplasia. All Class C ureters showed both hypertrophy and hyperplasia. In Class D, 17 of 18 ureters showed a greater than 100% increase in muscle area, and as muscle nuclei count ratio and total nuclei counts were increased in all cases, there was evidence of both hyperplasia and hypertrophy.

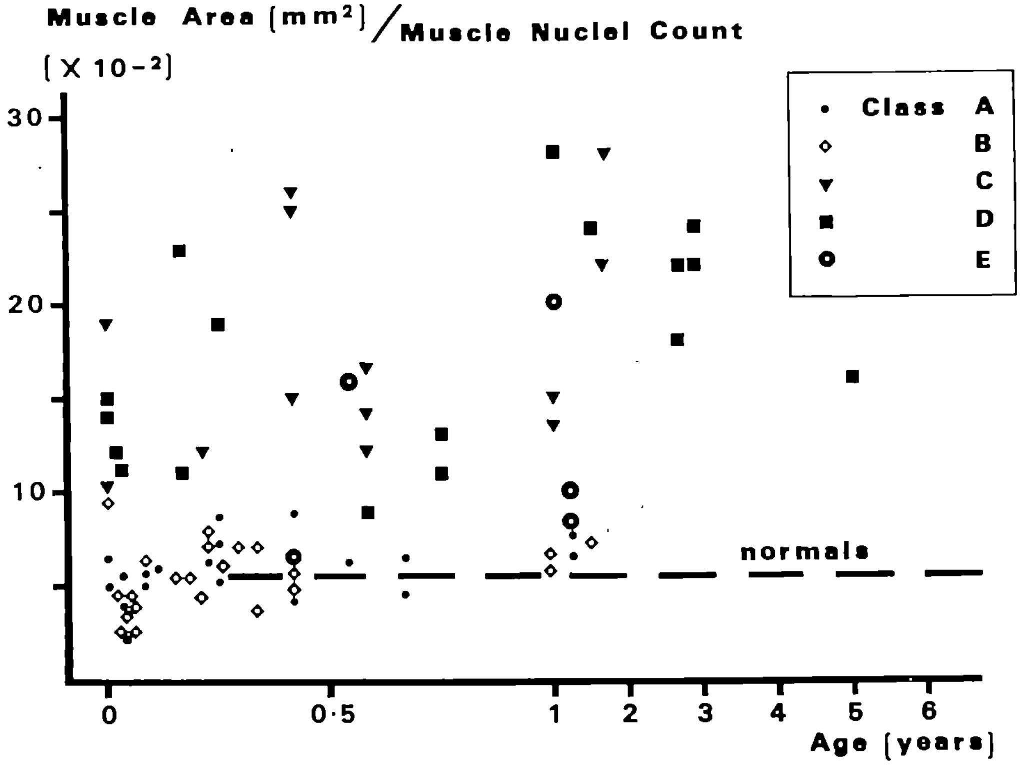

Fig. 4. The relationship of the muscle area to the muscle nuclei count related to age and the class of ureter deformity.

In Class E, 3 showed hyperplasia and hypertrophy, and 2 hyperplasia with no hypertrophy. The conclusion is that while all ureters of Classes C, D and E show hypertrophy of muscle, an increase in the number of muscle cells (hyperplasia) is more commonly seen in ureters of Class D.

Connective Tissue

Connective tissue area was estimated on the same sections of ureter as those used for muscle area determination. The results are shown in Table I and are related to age in Figure 5. Ureters in Class A are mostly in the normal range, whereas those in Class B characteristically show an increase in connective tissue.

The ureters with the highest connective tissue area (above 7 mm sq) are all of Class D, while those of Classes C and E show relatively little increase. There is, also, no obvious correlation between the amount of connective tissue and the age of the child.

Table I

Distribution of the Amounts of Fibrous Tissue in the Ureters of Different Classes

Connective Tissue Area (mm^2)	Class of Ureters				
	A	B	C	D	E
→ 1·9	16	8	...	...	...
2- 3·9	3	13	7	...	4
4- 5·9	...	1	5	3	1
6- 7·9	...	...	2	4	...
8-10·9	...	...	...	7	...
11-12	...	...	...	2	...
14-18	...	...	...	2	...
Totals	19	22	14	18	5

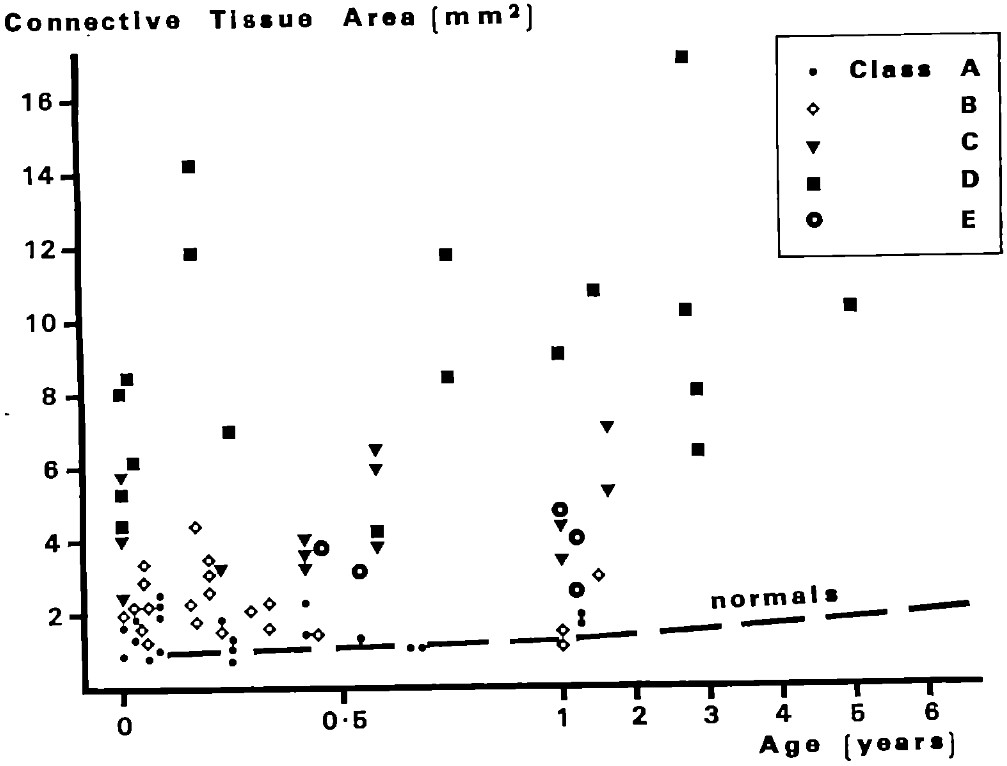

Fig. 5. The amount of connective tissue in cross-sections of ureters of different classes related to postnatal age, and to the mean of normals.

Elastic Tissue

Elastic tissue area estimated by the Point Counting technique represents the least accurate of the estimates, due to the variability of the staining properties of the very fine elastic fibres. The findings are shown in Table II, where both the amount of elastic tissue and its relation to the connective tissue are analysed. The elastic tissue does not appear to be increased in Classes A and B, but is most grossly increased in Class D, to a less extent in E and to an even lesser extent in C. When the ratio of elastic tissue to connective tissue is calculated, Classes C and D are similar whilst Class E shows a greater relative increase in elastic tissue.

The elastic tissue forms an almost complete ring in the adventitia with fibres penetrating between the muscle fibres. There is, however, often an apparent diminution in the number of very fine elastic fibres in the tunica propria, particularly in ureters with a greatly increased amount of connective tissue. In ureters of Classes C and D the increase in the amount of elastic tissue parallels the increase in collagen, but in the grossly dilated thin-walled Class E ureters the proportion of elastic tissue is higher. These findings tend to agree with the findings of Boone and Smith (1955), who found that the concentration of elastic fibres varies directly with the amount of collagen present, but are possibly not in accord with those of Stein and Weinberg (1962).

Table II

Amount and Range of Elastic Tissue in Different Classes of Ureter and its Relationship to the Amount of Connective Tissue

Class		A	B	C	D	E
Elastic Tissue area (mm^2)	Mean	0·08	0·08	0·39	0·94	0·56
	Range	0·00–0·43	0·00–0·54	0·08–0·70	0·03–2·99	0·12–1·18
Elastic-% C.T.	Mean	1·24	1·97	9	9·80	13·5
	Range	0·00–2·94	0·00–6·27	4·00–16·27	3·30–23·90	3·1–23·40

Intravesical Ureter Length and diameter

The lengths of the intravesical ureters in the various classes are related to crown to heel length in Figure 6 and to age in Table III. In ureters of Class A, only 1 of 19 showed a diminished intravesical length with respect to age. In Classes B, C and D, about 40% of cases showed a diminished length, while this was a consistent feature of all the Class E cases.

Gross Diameters of Ureters

The diameters of the ureters at the pelviureteric junction, at a point half-way from the kidney to the bladder, and at the ureterovesical junction are indicated in Table IV.

In all classes there is a tendency for the centre part of the ureter to be the most dilated area. There appears to be an association between the mean diameters at the ureterovesical and pelviureteric junctions, but this needs further investigation.

The Relationship between Types of Ureter and Causes of Renal Tract Deformity

In the cases selected for study, with the exception of 1 double ureter specimen, there was no recognised primary disease of the ureter throughout its whole length, though disease was present in other parts of the renal tract in all of them. 42 children had meningomyeloceles and 36 had a variety of conditions including bladder neck obstruction, absence of anus, megacolon and urethral valves.

Table III

The Intravesical Ureter Length in millimetres related to the Post-natal Age of the Child and the Relationship of the Intravesical Ureter Lumen to the Class Deformity

	Normals		Class A		Class B		Class C		Class D		Class E	
Age	No. of Cases	Mean (Range)	No. of Cases	Mean (Range)	No. of Cases	Mean (Range)	No. of Cases	Mean (Range)	No. of Cases	Mean (Range)	No. of Cases	Mean (Range)
0-1 mth	8	4·85 (4-6)	5	4·8 (4-5)	6	5·30 (3·5-7)	4	4·38 (2·5-5)	5	4·03 (1-8)		
1-6 mth	20	5·47 (4·5-7)	9	5·93 (1·5-10)	14	4·69 (2-7)	5	5·90 (3·5-7)	3	11·00 (8-16)	1	4 (—)
6-12 mth	4	6·20 (5-8)	3	6·5 (6-7)			1	5·00 (—)	3	5·00 (—)	1	1 (—)
1-3 yr	6	8·60 (6-10)	2	8·0 (—)	2	3·50 (3-4)	4	3·50 (2-5)	6	5·00 (2-9)	3	3·7 (2-5)
4-6 yr	12	8·30 (6-12)							1	3·00 (—)		
I.V.U. less than lower normal range			1 of 19 (5%)		9 of 22 (41%)		6 of 14 (43%)		7 of 18 (39%)		5 of 5 (100%)	
I.V.U. lumen diameter increased			2 of 19 (10%)		1 of 22 (4·5%)		5 of 14 (36%)		5 of 18 (28%)		5 of 5 (100%)	

Table IV

The Mean Intraluminal Diameters and Range of the Ureters

Class	Pelviureteric Junction Mean (Range)	Mid-point of Ureter Mean (Range)	Ureterovesical Junction Mean (Range)
Normal	1·22 (1-2·5)	2·0 (1-3)	1·27 (1-2)
Class A	1·4 (1-2)	1·85 (1-3)	1·57 (1-2·5)
Class B	2·7 (1·5-5)	5·25 (2·5-7)	2·42 (1-8)
Class C	3·6 (1·5-7)	5·7 (3-9)	3·0 (1·5-5)
Class D	4·9 (1·5-8)	8·5 (4-13)	4·5 (1·5-14)
Class E	7 (5-13)	11·4 (7-15)	6 (1-13)

The normal ranges were obtained in our previous study.

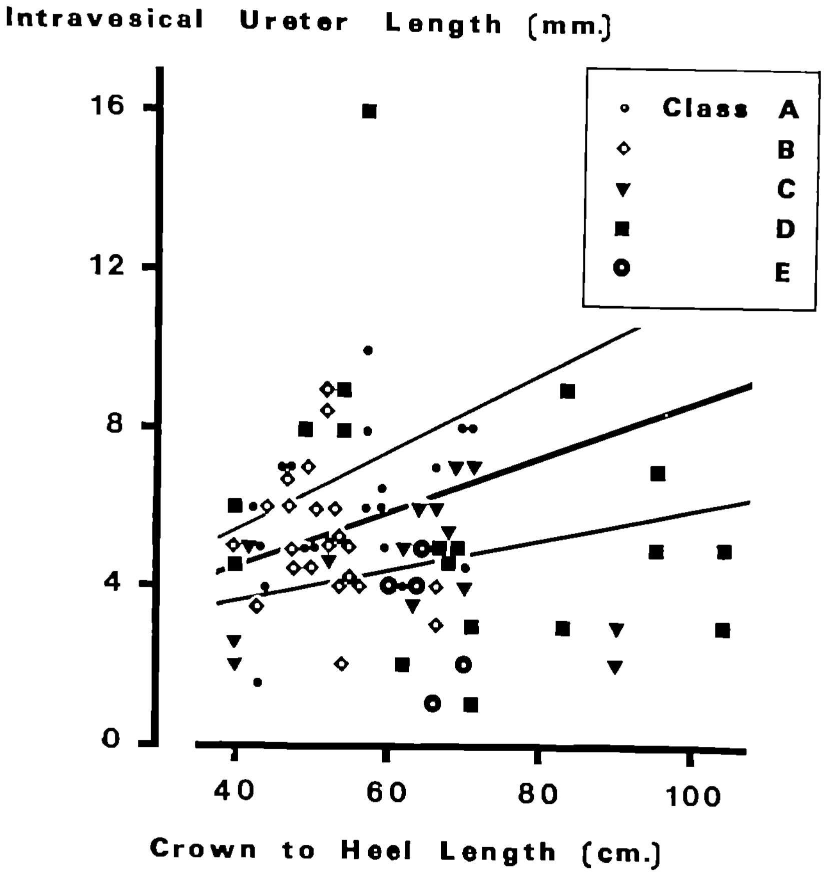

Fig. 6. The intravesical ureter lengths of ureters of different classes related to crown to heel length. The distribution is superimposed on the mean and 100 percentile lines from normal children of the same height. Note the extreme variability of the findings, particularly in relation to ureters Class D.

In 10 children the right and left ureters were sufficiently different for each to be classified differently, but it was not possible to generalise on the evidence available of an association of any ureter class with a constant bladder or renal pathology. The children with meningomyelocele showed the widest variation—Class A, 8; Class B, 14; Class C, 11; Class D, 4; Class E, 5. Children with urethral valves occupied Classes C and D only and children with bladder neck obstruction occupied Class D only.

The Relationship of Local Structure to the Form of the Ureter

Ureters in Class B were the only ones showing variations in structure in different areas. Several of them were examined throughout their length in an attempt to compare the components of the constricted and dilated areas, particular search being made for connective tissue and abnormal alignment of muscle bundles in the narrow segments. In none of the specimens could it be convincingly shown that there was any certain difference in the amount of muscle, elastic tissue or connective tissue in the narrower or the dilated areas.

Discussion

Of the elements measured in these ureters the muscle and muscle nuclei are the most clearly defined and most accurately measured. The connective tissue is well defined but there are essential errors in the outer limits of the tissue measured. The elastic tissue is least accurately measurable due to some variability in staining in long fixed tissues and the difficulty in identifying very fine fibres.

This study was carried out in an effort to produce a basis for the classification and study of apparently secondary type of ureteric abnormalities in children. We have attempted to make use of a large amount of material but, as we have no knowledge of the pressure within and function activity of the ureters during life, the detailed analysis of individual cases is of limited value.

In our classification the Class B ureters appear to be intermediate between A and the other 3 groups, which will therefore be discussed first.

The Class C ureter (so-called, but probably falsely, the "lead-pipe" ureter) has a particular quantitative structure in that there is a moderate degree of dilatation associated with a great increase in the amount of muscle and a moderate increase in the amount of connective tissue. The amount of elastic tissue is increased proportionally to the connective tissue.

The Class D ureter has a greater intraluminal diameter and this is associated with an increase in length, which would seem to be the linear component of the transluminal component of the dilatation. The ureter is thus dilated both longitudinally and laterally and therein lies its essential difference from Class C ureters. There is both hypertrophy and hyperplasia of muscle, a considerable increase in elastic tissue, but an even greater increase in the amount of connective tissue.

In ureters of Class E the luminal parameters, both longitudinal and transverse, are out of complete proportion compared with the muscle, connective tissue and elastic tissue of the ureter wall.

If we consider that the function of the muscle of the ureter is to form a regulatory system of variable pressures down the ureter, the mechanical effect of the muscle on the intraluminal pressure will be very greatly affected by the diameter of the lumen. It is questionable how much the La Place formula will apply to the ureter, but the principle undoubtedly does. Thus the amount of muscular activity required to maintain an intraluminal pressure, if the diameter is doubled, is not twice the muscular strength but a square of it (Burton, 1957; Roach and Burton, 1957; Burton, 1966). To maintain an intraluminal pressure control of a ureter of average diameter of 5·7 mm (Class C) over the diameter of the normal ureter (Class A) or the normal, which is 2 mm, will require approximately a 10-fold increase in the muscle strength, which is not far from the increased bulk of muscle that we observe in Class C ureters. Thus it seems that the type C ureter could well be one in which, because of an increased luminal diameter, there has been compensatory hypertrophy and hyperplasia of muscle.

In ureters of type D and E we are dealing with structures in which such a muscle-lumen pressure balance is not possible and which are muscularly essentially incompetent. Such ureters could therefore only function as reservoirs and probably could not control the direction of flow of urine under any normal intra-ureter pressure states.

The general function of elastic tissue is considered to be that of controlling the rate of change in the form of a tissue, whereas collagen limits the extent of such change. The grossly dilated tortuous category E ureters are the ones with a relatively great increase in elastic tissue over fibrous and muscular tissue and seem to function as a rather mobile bag or elastic stocking. They do, however, contain an increased amount of connective and elastic tissue and also an increased amount of muscle as compared with the normal ureter in category A. Thus, if they could be allowed to function at a greatly reduced pressure so that their lumens could return to almost normal size (*i.e.* in the region of 1 to 3 mm), they have enough muscle to allow them to function as normal muscular ureters. This presupposes a normal nervous element supplying the muscles.

A Class E ureter, therefore, appears to be completely decompensated, Class D is partially compensated and Class C is probably fully compensated. Class B ureters are best considered as being intermediary between Classes A and E as they have essentially normal quantities of muscle with relatively little increase in fibrous and elastic tissue and appear to be eminently capable of functioning as normal ureters once they are permitted to regain their normal luminal diameter.

The question that immediately arises is what makes one ureter acquire a form either of Class E or Class C. Once a ureter acquires the characteristics of Class E, the chance of it ever acquiring a compensatory hypertrophy to control its activity is unlikely. It is likely that a ureter would become Class C only when it has been subject to gradually increasing rather than to an acute overwhelming stress.

It is possibly significant that the only group of ureters in which we found obviously patent and incompetent ureterovesical junctions was in Class E. The microanatomy of this area has been a source of discussion and controversy since Waldeyer's day (Waldeyer, 1892) and has been the subject of many limited investigations. From the studies of our own material (both the normal and the abnormal) we believe that the subject has probably been grossly oversimplified and that Hutch (1961) and others have been misled by examining a few selected specimens and assumed a general theory of maturation of the intravesical ureters (Stevens and Lenaghan, 1962; Tanagho and Pugh, 1963; Tanagho, Hutch, Myers and Rambo, 1965; Woodburn, 1965; Lenaghan and Cussen, 1968). Our studies of normal ureters showed a progressive lengthening of the intravesical ureter with age in step with the lengthening of the whole ureter. We have also shown that though shortening and increased luminal diameter (*i.e.* apparent permanent patency of the ureterovesical junction) occurs in some cases where there is gross abnormality of the ureter, this certainly does not always apply.

The only really valid dynamic study of the elastic properties of the ureter appear to have been carried out by Boone and Smith (1955), whose findings suggest that the elastic properties of the ureter diminish with age and that the normal ureter appears to have a very great resistance to transmitted back pressure.

Perhaps the most interesting aspect of the ureter is the uniformity of change throughout its whole length. The whole of the musculature of the ureter is contained within a very extensive continuous fine nervous plexus so that every muscle bundle is sheathed with fine nerve fibres, and this applies to all normal and abnormal ureters that we have studied. The scanty small nerve cells present (Forbes, Underwood and Emery, 1970) could not control the overall activity of a peristaltic wave throughout the whole length of the ureter.

We have found no nodes such as cardiac muscle pacemakers as postulated by Murnaghan (1957) and Notley (1970) and have no anatomical explanation as to why parts of group B ureters are more contracted than others. We still need to know more of the function of the elastic tissue in ureters and the work of Boone and Smith (1955) needs greatly extending on the lines of work done on blood vessels in different parts of the body.

Summary

A gross and quantitative study of the muscle and connective tissue and elastic tissue has been carried out on a series of 78 abnormal ureters in children.

The ureters have been classified into 5 classes: (A) normal; (B) ureters with irregular dilatations; (C) slightly dilated ureters with muscular hypertrophy and hyperplasia; (D) elongated and dilated ureters with muscular hypertrophy and hyperplasia but probably decompensated; (E) grossly distended and elongated ureters having an increase in elastic tissue but with no comparable muscular hypertrophy or hyperplasia.

Ureters showing structural changes do so uniformly throughout their length and no local anatomical deformities were found to account for the irregularities in the ureters of Class B.

Structurally incompetent uretero-vesical junctions are only associated with ureters of Classes D and E.

All abnormal ureters show varying degrees of muscular hypertrophy and hyperplasia. It is suggested that the form of the ureter is related to whether or not the muscular hypertrophy is adequate to compensate for the increased luminal diameter.

This investigation was carried out with the aid of a grant from Action for the Crippled Child and from The Richard Fund.

Photographs by Mr A. Tunstill.

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The Post-natal Development of the Muscle and Connective Tissue of the Normal Ureter—A Quantitative Study

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Knowledge of the structure and function of the ureter is incomplete. The mechanism of control of ureteric function is under dispute. Following the treatment of hydrocephalus in children with neurospinal dysraphism, an increasing number of children are surviving the neonatal period to succumb to renal disease, apparently secondary to paralytic disorders of the ureter and bladder. In order to assess changes that may be the result of paralytic disorder of the renal tract it is necessary to have a critical knowledge of the normal structure at different ages during childhood.

Whilst some workers have included normal children in their surveys of ureters (Gerard, 1908; Satani, 1919; Nixon, 1929; Boone and Smith, 1955; Hutch, 1961; Stein and Weinberg, 1962; Monticone, 1940) only one quantitative study of normal ureters in childhood has been reported (Cussen, 1967). Cussen studied ureters from children varying in age from 12 weeks' gestation to 12 years. Ureter dimensions were measured on unfixed material. Muscle areas and number of elastic fibres (apparently regardless of area occupied) were calculated from estimates made on limited areas of transverse sections through the ureter wall. No attempt was made to quantify collagen fibres present. The size of individual smooth muscle cells was estimated from muscle nuclei counts within a known muscle area.

In the present survey a more sophisticated point-counting method of tissue area determination was employed, that enabled the estimation of the area of all tissue components present in the ureter wall.

Material and Methods

50 ureters obtained at necropsy from children (age range 0 to 6 years) were examined. These came from children in whom there was no suspicion of renal tract disease or of central nervous system disease likely to affect the ureter or bladder. The bladder was emptied at necropsy and distended *in situ* with 25 ml of formalin. This procedure enabled a parallel study to be made of bladder musculature (Forbes, 1970). The whole bony pelvis and contents were then removed. The ureter measurements were made on renal tracts fixed *in situ*. Only renal tracts which were macroscopically normal and did not demonstrate vesico-ureteral reflux at necropsy were selected.

The ureters were dissected clear and measurements taken from the pelvi-ureteric junction to the bladder using a metal ruler and soft copper wire. The ureters were cut transversely into 1-cm segments and the intraluminal diameter of each segment measured by insertion of standardised stainless steel probes. The diameter recorded was that of the largest probe which could be inserted without stretching the wall of the ureter which in the fixed state is virtually non-elastic. A block of tissue including the uretero-vesical junction was removed from the bladder and the total length of the intravesical ureter measured by insertion of a fine graduated probe.

The 1-cm segments of ureter were processed, and embedded in paraffin wax and sections cut at 6 microns. The sections were stained with haematoxylin and eosin, Heidenhain's Iron Haematoxylin, Masson's Trichrome, Verhoeff's Elastic/Van Gieson and Gomori's Aldhyde Fuchsin/Van Gieson. It was found that Verhoeff's Elastic/Van Gieson staining gave the best contrast between muscle (yellow), collagen (red) and elastic tissue (black) and this stain was preferred for tissue area determination. It was found that the quality of the fixed tissue in some specimens did not permit the general use of more specific staining methods.

A complete survey of the tissue components present in transverse sections of the ureter wall was carried out at high magnification (× 100 oil immersion objective) using a Swift Automatic Point Counter (Chayes and Fairbairn, 1951; Hally, 1964; Humphries, 1969).

Since accuracy of a point-sampling method depends mainly on the number of points counted and also the proportion of any one tissue component present, muscle area was selected as a reference. The distance between adjacent points was adjusted to give a large enough count on muscle to maintain a relative standard error of less than 0·15.

E.g. Muscle area (mm^2) = muscle count × (vertical × horizontal) microscope stage stepping distance between adjacent points (mm). $0{\cdot}50\ mm^2 = \text{muscle count} \times 0{\cdot}157 \times 0{\cdot}053$ Muscle count $= 0{\cdot}5/0{\cdot}008 = 63$

$$\text{Relative Standard Error} \leqq \frac{1}{\sqrt{n}}, \text{ where } n = \text{muscle count}$$

$$= \frac{1}{\sqrt{63}}$$

$$= 0{\cdot}126$$

$$\therefore \text{ Muscle area} = 0{\cdot}50 \pm 0{\cdot}063\ mm^2.$$

Cussen attempted to estimate the size of individual muscle cells by counting muscle cell nuclei visible through the section thickness (10 μ) and relating this count to a unit volume of muscle. This method is accurate only if the true density of nuclei is known (Abercrombie, 1946). Since the main reason for counting muscle cell nuclei is to determine whether hypertrophy or hyperplasia of muscle cells occurs with increasing muscle area, it was decided to record points landing on muscle nuclei separately from other muscle counts and to investigate the relationship between muscle area and muscle nuclei counts, rather than use the laborious but accurate methods proposed by Abercrombie.

Results

Ureter Length

Ureter length was correlated with age, weight of the child, sitting height (crown to rump length) and total height (crown to heel length).

A plot of ureter length against age is shown in Figure 1. At birth the ureter was 6·5 cm long, increasing to 12 cm at the age of 2 years and 14 cm at the age of 6 years, the greatest rate of increase in ureter length being in the first 2 years. The growth curve is very similar to that observed by Cussen, who reported unfixed ureter lengths.

The relationship of ureter length to crown to heel length (Fig. 2) was linear over the age range examined. It was found that:

$$\text{Ureter length (cm)} = 0{\cdot}125 \text{ of C to H length} + 0{\cdot}5 \text{ cm.}$$

Three measurements only deviated more than 1 cm from this mean line, the largest deviation being 2·2 cm.

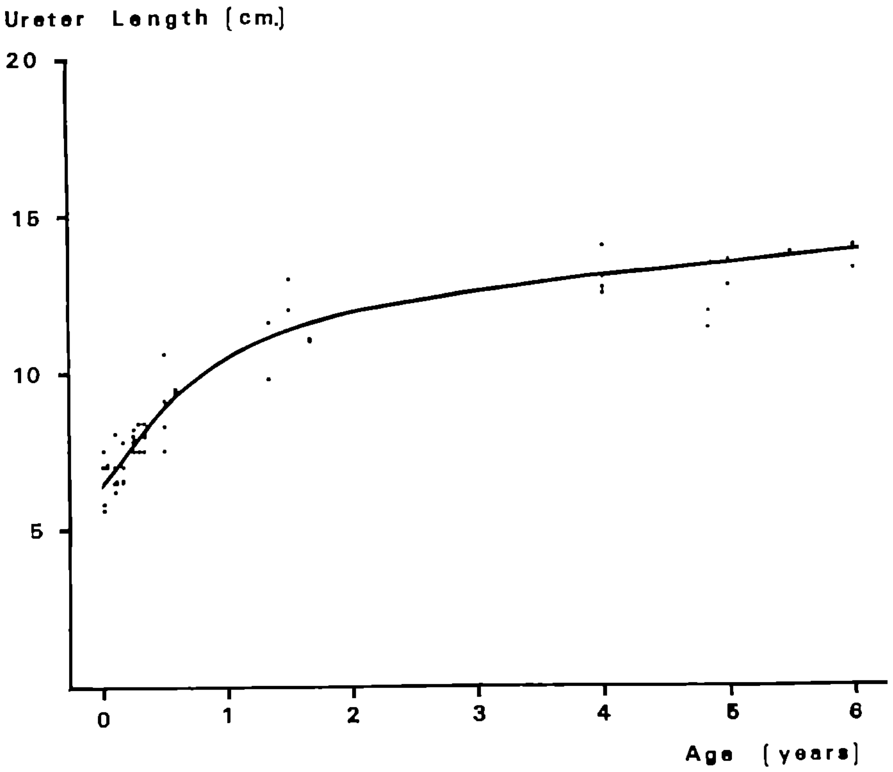

Fig. 1. Graph of the extravesical ureter length (cm) related to post-natal age (years).

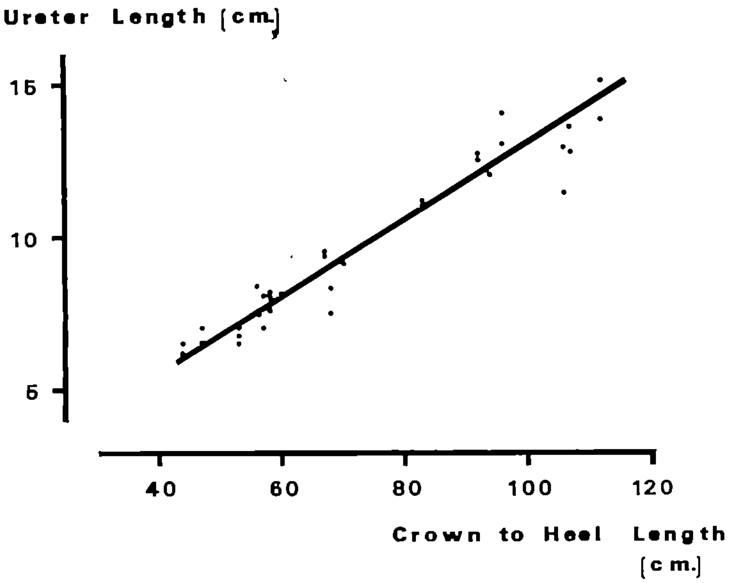

Fig. 2. Graph of extravesical ureter length (cm) related to crown to heel length (cm).

Table I

Mean Intraluminal Diameter and Range (mm) at the Pelviureteric Junction 0·5 of the Distance down the Ureter and Uretero-vesical Junction at Different Ages

Age	Number of Cases	P.U.J.		0·5 Distance down Ureter		U.V.J.	
0-1 wk	4	1·62	1-2	2·2	1·5-3	1·2	1-1·5
1 wk-1 mth	10	1·2	1-1·5	1·85	1-2 5	1·35	1-2
2-3 mth	3	1·0	. .	2·17	1·5-2·5	1·3	1-2
4-6 mth	10	1 0	1-1·5	2·0	1·5-2·5	1·3	1-2
7 mth-1 yr	6	1·1	1-1·5	1·85	1-2·5	1·33	1-2
1-2 yr	5	1·4	1-2·5	1·8	1-2·5	1·2	1-1·5
4-5 yr	6	1·15	1-1·5	2·0	1·5-2·5	1·25	1-2
5-6 yr	6	1·33	1-2	2·25	1·5-3	1·33	1-1·5

Table II

Mean Length of Intravesical Ureter and Range (mm) at Different Ages

Age	Present Series			Hutch			Cussen	
Prematures				(4)	22·5	[1-4]	3	[2-5]
0-1 wk	(4)	4·5	[4-5]	(6)	5	[4-6]	4	[2-7]
1 wk-3 wk	(4)	5·2	[5-6]					
2-3 mth	(10)	5·45	[4·5-6]				5	[2-9]
4-6 mth	(10)	5·5	[4·5-7]					
7-12 mth	(4)	6·2	[5-8]	(2)	7	[7-8]	7	[4-13]
2-3 yr	(6)	8·6	[6-10]	(2)	5·5	[5-6]	7	[4-9]
4 yr	(6)	7·2	[6-9·5]					
5-6 yr	(6)	9·4	[7-12]	(2)	8·5	[8-9]	7	[4-12]

Numbers in round brackets indicate number of ureters studied.
Numbers in square brackets indicate range of intravesical ureter length.

Table III

Mean Length of Intravesical Ureter and Range (mm) at Different Crown to Heel Lengths (cm)

Crown to Heel Length	Number of Cases	Mean I.V. Length	Range
40-50	5	5·2	4-6
50-60	18	5·42	4-7
60-70	6	5·7	4-8
70-80	...	...	...
80-90	2	7·5	6-9·5
90-100	6	8·0	6-10
100-110	4	9·5	6-12

Intra-luminal Diameter of Ureter

Mean measurements and range (mm) at P.U.J., 0·5 distance down the ureter and U.V.J. for different age-groups are given in Table I.

The intra-luminal diameter was greatest at 0·5 of the distance down the ureter. The diameter at all 3 sites tabulated showed no significant change during the period from 0 to 6 years in fixed ureters.

Intravesical Ureter Lengths

The measurements of the intravesical ureter lengths with the ranges are shown in Table II, where our results are compared with those of Hutch and of Cussen.

A plot of the intravesical ureter length against crown to heel length (Fig. 7) shows an essentially linear relationship over the range investigated.

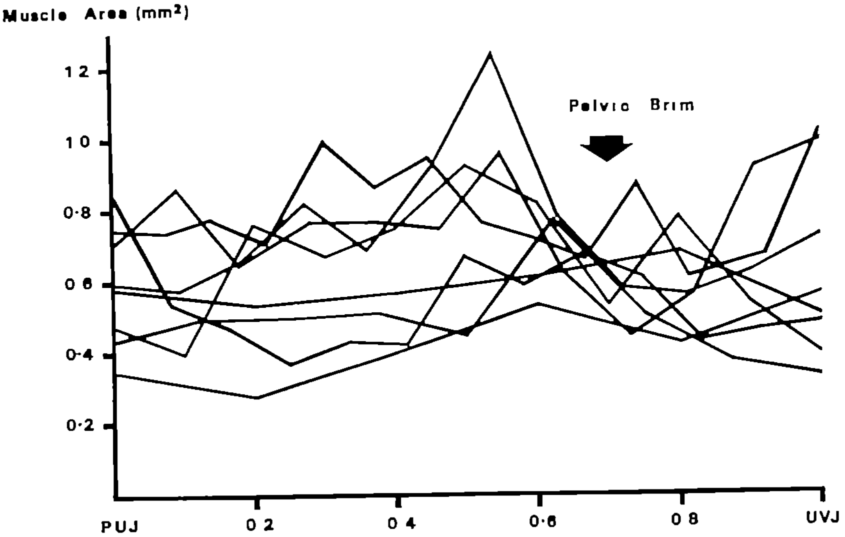

Fig. 3. Graph showing the amount of muscle (mm²) in 8 ureters from children of different ages combined on the basis of percentage distance down the ureter from pelvi-ureteric junction to the uretero-vesical junction.

Variation in Muscle and Connective Tissue Area down the Ureter

In 8 children spanning the age range examined, serial blocks were taken at 1-cm intervals throughout the length of the ureter and each level quantitated for the amount of muscle and connective tissue. Variation in muscle area down the ureter is shown in Figure 3, where the lengths of the ureters have been standardised on a percentage basis to compensate for the growth of the ureters in older children.

There appear to be irregularities in most of the ureters but these are probably of little significance. Any variation in obliquity of the transverse section of the ureter is liable to give an increased reading to the muscle area count and this may account for the small peaks in a number of the ureters. Variation in muscle area between different ureters is most noticeable at one-third of the distance down the ureter and at the uretero-vesical junction. There appears to be least variability in the values of muscle in the region of the pelvic brim, where the ureter is relatively straight as it courses over the psoas muscle.

The graph showing the combined muscle areas of children dying over the age of 4 years and under the age of 4 years (Fig. 4) suggests that muscle area is maximal in its middle third but that there is fair uniformity in dispersal of muscle.

Estimates of combined connective tissue areas show a similar pattern to that of muscle areas.

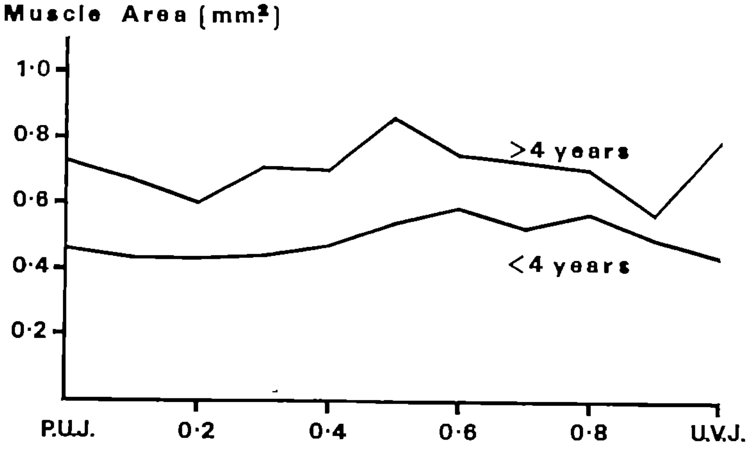

Fig. 4. Graph showing combined muscle areas (mm²) of children over 4 years and under 4 years of age (expressed as in Fig. 3 as percentage distance along the ureter).

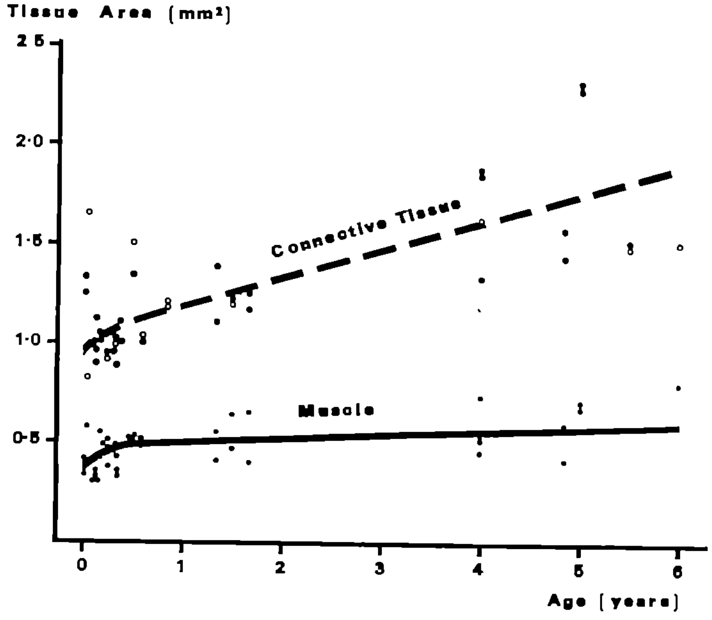

Fig. 5. Mean muscle and connective tissue areas (mm²) in transverse sections of ureter wall related to age (years).

Growth of Muscle and Connective Tissue

The mean areas of muscle and connective tissue in transverse sections of ureters related to age are shown in Figure 5. Mean muscle area was 0·38 mm² at birth rising to 0·50 mm² at 1 year and 0·60 mm² at 5 years. Mean connective tissue area was 0·95 mm² at birth rising to 1·2 mm² at 1 year and 1·75 mm² at 5 years. Whereas muscle area increased by approximately 58% during the first 5 years, connective tissue area increased by 84% during the same period. Muscle area expressed as a percentage of muscle and connective tissue was approximately 30% at birth and 40% at 5 years.

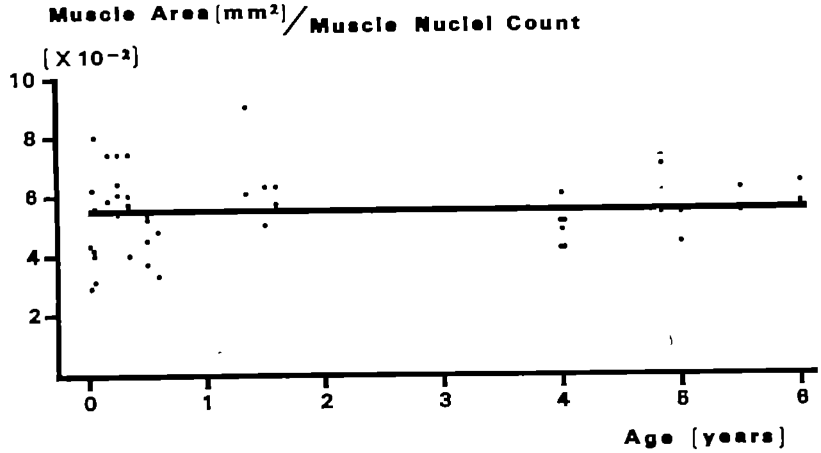

Fig. 6. Ratio of muscle area (mm²) to muscle nuclei count related to age.

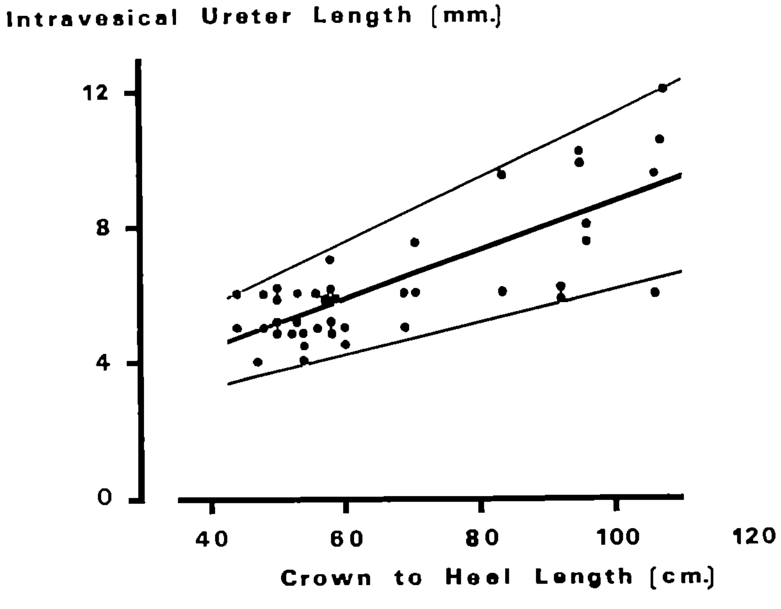

Fig. 7. Graph of intravesical ureter length against crown to heel length.

The Size of Muscle Cells

The ratio of muscle area to the number of nuclei remained constant (Fig. 6). Thus, there is no evidence for any increase in the mean size of muscle fibres over this period in the normally growing child. The ureter length and consequently the muscle bulk is increasing considerably during this period; therefore, it must be postulated that new muscle cells are being formed, either by differentiation of mesenchymal cells or by proliferation of existing muscle cells, at the same rate as ureter elongation.

Elastic Tissue

Elastic tissue area of normal ureters was too small for numerical estimate using the Point-Counting technique at an acceptable level of accuracy. In some ureters we were unable to demonstrate any elastic fibres. In ureters where elastic fibres were demonstrated they appeared poorly developed in the submucosal and muscle layers and thicker and more numerous in the adventitia surrounding the ureter.

Discussion

The overall growth of the normal ureter appears to be directly related to the height of the child and less closely related to age or body weight—a feature well known in other body criteria. Within the height range studied, only 3 ureters deviated more than 1 cm from a straight mean line, which can be represented by the formula:

$$\text{Ureter fixed length (cm)} = 0{\cdot}125 \text{ crown to heel length} + 0{\cdot}5.$$

Cussen plotted mean ureter lengths over 20-cm intervals against height (cm). His results show a slightly irregular distribution of mean figures but he also shows almost a linear relationship which can be represented by the formula:

$$\text{Ureter length (cm)} = 0{\cdot}175 \text{ crown to heel length (cm)} - 1,$$

which gives an unfixed ureter length which is approximately 10% longer than our result at a crown to heel length of 50 cm rising to 20% longer at crown to heel length of 100 cm. Formol fixation involving muscle and connective tissue causes about 10% shrinkage. Unfixed ureters are capable of considerable stretching and this is the most likely cause of the discrepancy of the 2 sets of results at longer ureter lengths. It would appear that both formulae are valid and should be applied, 1 to the unfixed state and the other to the fixed state.

Since the intravesical ureter is mobile within the bladder wall, its length is probably dependent on the degree of inflation of the bladder. Comparative studies of intravesical ureter length are valid only if the bladder is uniformly distended and the intravesical and pelvic ureter fixed *in situ*.

Our results using this procedure indicate a progressive increase in intravesical ureter length, with increase in age and crown to heel length. We could find no significant alteration in the form of the uretero-vesical junction within the age-group studied.

The distribution of muscle through the length of the ureter (Fig. 3) indicates that there is least variability in the region of the pelvic brim and this area could best be taken for sampling of ureter musculature. This relative uniformity of the ureter around the pelvic brim coincides with the apparent area of constriction noted by Nixon (1929) in his study of 51 normal adult ureters.

The growth of ureter muscle appears to be uniform throughout its whole length. The proportion of muscle in the ureter wall increased from 30% at birth to 40% at 5 years. These results are in agreement with Stein and Weinberg, who found muscle, 35% stillborns and 50% in adult ureters. We were unable to identify with certainty any definite zoning of muscle in any individual section. No groups of muscles were identified analogous to Purkinje cells in the heart as postulated by Murnaghan (1957, 1959), who believes that areas of muscle have inherent pacemaker abilities.

The connective tissue shows a progressive increase with age, and, similar to the muscle area, is least variable at the region of the pelvic brim. The proportion of connective tissue relative to muscle decreases with increasing age—a feature common to most developing organs.

The development of elastic tissue in the ureter requires further study. We were unable to report on the quantitative development of elastic tissue because of the variability of staining proportion and the limitations of the point counting technique employed in this study. Boone and Smith (1955) found elastic fibres in the adventitia but variable results in the submucosal and muscle layers of ureters from normal children. Stein and Weinberg (1962) report more elastic tissue in the tunica propria than in the adventitia in stillborns (20 to 40 weeks' gestation). Cussen (1967) found that elastic fibres appear at the time of birth in the region of the middle spindle, but found poor correlation with increasing age in the first twelve years of life.

Summary

A quantitative study of the muscle and connective tissue using a Point-Counting technique and measurements of the extravesical and intravesical ureters was carried out on normal ureters from infants and children (age range 0 to 6 years).

Ureter growth—both intra- and extravesical—was found to be directly proportional to the height of the child. There is progressive development of muscle and connective tissue. During the period from 0 to 6 years the growth of muscle appears to be due to a progressive increase in the number of muscle cells. Normal values are presented for intravesical and extravesical ureter length and musculature.

This investigation was carried out with the aid of a grant from Action for the Crippled Child.
Photographs by Mr A. Tunstill.

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Nephrogenic Adenoma of the Bladder

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This paper reports an example of the rare disorder "nephrogenic adenoma" of the urinary bladder.

Case Report

On 25th December 1969 a youth of 16 was admitted to hospital after sustaining a severe head injury in a road accident. He was deeply unconscious and there were multiple bruises and lacerations. During a prolonged period of recovery he was very spastic and exhibited minor fits and convulsions. An indwelling urethral catheter was necessary and later haematuria was noted and a *Proteus* infection of the urine developed. He was discharged on 9th March 1970. In July 1970 he complained of severe dysuria and was re-admitted for urological investigation. The urine was sterile and contained no pus cells, while cystoscopy revealed only a slight, patchy hyperaemia of the trigone.

In January 1971, a year after his injury, he attended the Urological Clinic complaining of persistence of the dysuria. He had severe pain during and after micturition, maximal at the end of the penis. There was no frequency but haematuria took place on a few occasions. His blood pressure was 130/90 and examination of the genito-urinary system was negative.

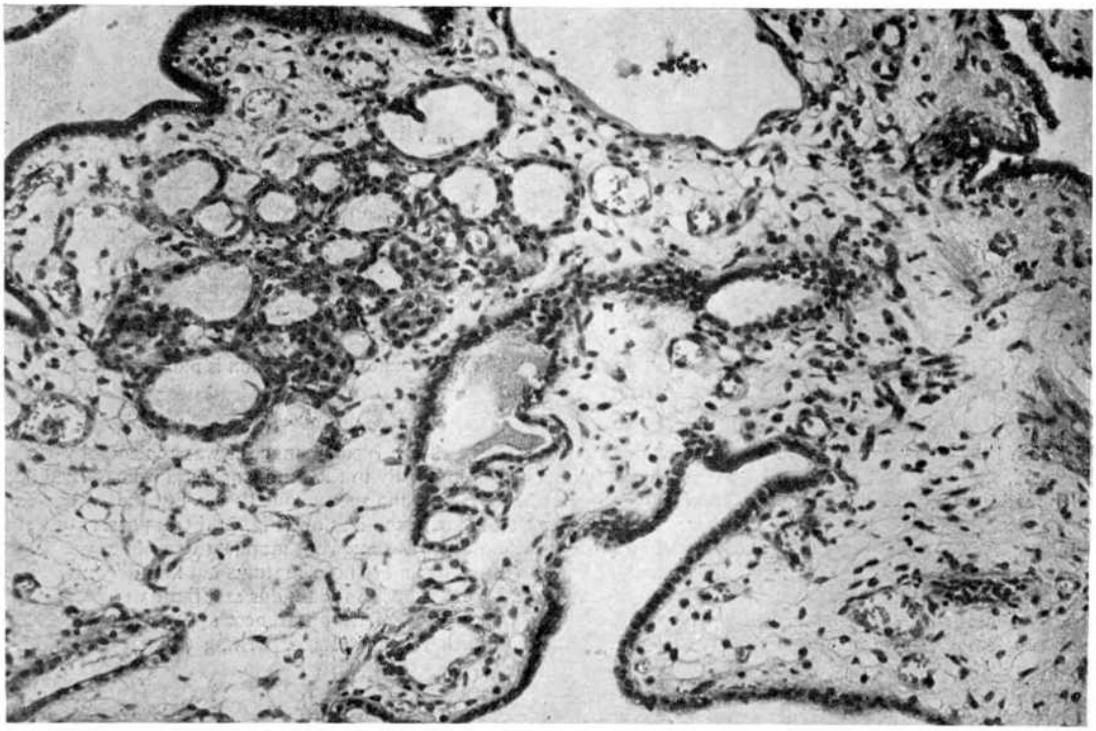

Fig. 1. High power view of bladder lesion (first biopsy). Note the tubular structures lined by a single layer of cubical epithelium.

Investigations

Mid-stream specimen of urine—normal. Serum urea—20 mg %. Blood count normal. Examination of urine for tubercle bacilli—negative. X-ray of chest—normal. I.V.P. showed normal kidneys but some irregularity of the outline of the bladder base.

Cystoscopy showed 3 small papillomatous lesions in the bladder mucosa. A biopsy was reported—"The histology is very interesting. It suggests a pedunculated adenoma of nephrogenic type and appears to be quite benign. It is covered mainly by cubical, partly by transitional epithelium. The fibrous core contains glandular spaces somewhat resembling renal tubules and telangiectatic, almost haemangiomatoid vessels." (Fig. 1.)

We were at a loss to know how to deal with this unusual disorder and it was decided to keep the patient under observation for a time without treatment. In September 1971 he was re-admitted with the symptom of painful micturition unchanged. There had been no further haematuria. At a further cystoscopy on 23rd September 1971 it was clear that the number of lesions in the bladder had increased in number and size. Several red, smooth, nodular swellings could be seen, mostly in the fundus. Biopsy was repeated and the same histological appearances found.

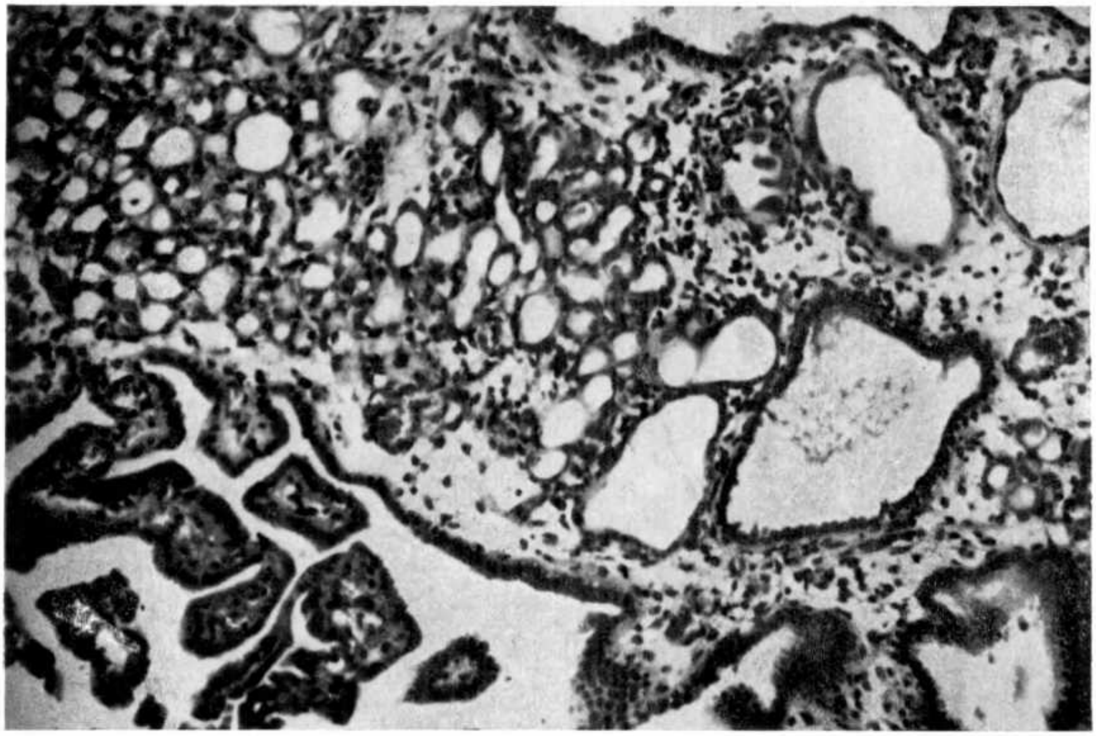

Fig. 2. High power view of bladder lesion (operation specimen). The adenomatous proliferation is more active.

Operation

On 30th September 1971 the bladder was explored. About 1/5th of the bladder mucosa was replaced by pink, elevated, shiny swellings varying 0·2-3·0 cm in diameter. They were mostly in the fundus: several were excised but the smaller ones were diathermised. There was no sign of invasion of the submucous tissues but the latter were quite oedematous. A satisfactory recovery followed. On histological examination (Fig. 2) the appearances were similar to those found on biopsy but the adenomatous proliferation was somewhat more active and irregular.

The patient was seen in February 1972. There had been an improvement in his symptoms but he still complained of some discomfort on micturition. Cystoscopy revealed a few tiny lesions in the fundus and these were destroyed by cystodiathermy. A further cystoscopy on 11th May 1972 revealed similar appearances and further diathermy was performed. Six weeks later only a few small lesions remained. At the time of writing (January 1973) the bladder looks normal.

Some of the features of this case warrant emphasis. The predominant complaint was pain during and after micturition: there was little frequency and only occasional haematuria. Despite the insistence by the patient on the severity of his symptoms there was a delay of between 6 and 12 months before any lesions were visible on cystoscopy, but once they began to form they increased in number and size fairly rapidly. The submucosal oedema under the lesions was noteworthy, and the response to diathermy satisfactory. The infection previously present in the urinary tract had disappeared before the bladder lesions made their appearance.

Comment

Previous Cases of "Nephrogenic Adenoma" of the Bladder

In 1950 Friedman and Kuhlenbeck drew attention to an interesting, but very rare affection of the urinary bladder. Tumour-like masses formed in the lining of the organ and histological examination revealed a papillary appearance, but in addition there were tubules and cystic structures. The tubules were lined by a single layer of cuboidal or low columnar cells, and the general resemblance to renal tubules led to speculation that the lesion was attributable to latent histogenetic potency of nephrogenic type in the mesodermal element of the bladder mucosa. Consequently the term "nephrogenic adenoma" was applied to the lesion. The authors drew their material from the collection of the Armed Forces Institute of Pathology of the United States of America, 7 out of the 8 patients being young males.

Mostofi (1954), in a discussion of the potentialities of bladder epithelium, mentioned a personal communication from R. A. Holmes describing the development of a small tumour in the bladder some time after injury to the organ. Little clinical information was supplied, but histologically the appearances were exactly those of the case described by Friedman and Kuhlenbeck. Mostofi felt that the lesions should be interpreted as a manifestation of metaplastic behaviour of vesical epithelium.

Hasen in 1962 described an interesting example of the same condition. A 22-year old male was treated for intra-abdominal rupture of the bladder and other injuries. Suprapubic and urethral drainage was maintained for 20 days, and this was followed by urinary tract infection which was resistant to all forms of treatment. Six years later he complained of haematuria, and cystoscopy—which previously had been negative—revealed 2 dark red mulberry-like lesions each 1 cm in diameter in the dome of the bladder. Biopsy showed glandular spaces assuming a renal tubular pattern. The tubule-like spaces were lined with single rows of cuboidal or columnar epithelium, similar to those lining the loop of Henle, distal or collecting tubules or mesonephric ducts. The lesions were diathermised and cystoscopy the following year showed the bladder was clear.

Davis (1949) described a similar case under the title "Hamartoma of the Urinary Bladder". His patient, a male aged 40 years, presented with a year's history of frequency, burning, perineal pain and haematuria. The urine was infected. There was no history of injury. The bladder mucosa had numerous granular-appearing areas, somewhat elevated and strawberry-like in appearance. Histologically the tumours had a generally papillary structure, the processes being covered with low cuboidal epithelium. In addition there were gland-like and cystic structures. Treatment directed to infection was ineffective. The lesions increased in number until treated by repeated cystodiathermy which eventually cleared the bladder and relieved the patient's symptoms. Infection of the urine by B. Friedlander proved difficult to eradicate.

Goldman (1972) has recently described 3 additional examples of this disorder. Each patient was an elderly male with evidence of chronic infection to the lower urinary tract. In 2 patients the lesions were discovered at autopsy. They were solitary and situated on the trigone and posterior bladder wall respectively. In the third case the lesion was found in a patient undergoing transurethral resection, and was removed from the trigone with the resectoscope.

Together with the case report in this paper, the above appear to be the only examples of nephrogenic adenoma of the bladder which have appeared in the literature. Adenomata of the bladder are described from time to time, *e.g.* by Merkelbach in 1965 and Salm in 1967, but the histological pattern is completely different from the one we are dealing with here. Moose and Garvey (1963) reported a case of hamartoma of the bladder which also is an entirely different lesion. Dr K. M. Cameron of the Department of Pathology, St Peter's Hospital, London (personal communication) says that a number of examples of "nephrogenic adenoma" have been seen in the Department in recent years. Most of the patients had a history of either Hunner's ulcer or genito-urinary tuberculosis.

Discussion

Although the clinical material relative to this rare disorder is meagre, it is possible to extract a picture of a fairly characteristic clinical and pathological entity. The bladder lesions are red in colour and likened to strawberries or mulberries, and are elevated above the surface of the mucosa; often shiny in appearance and with a smooth surface. They bleed when touched. Our case was the only example in which open operation afforded opportunity for direct examination, and we were impressed by the oedema of the underlying bladder wall. The intervening mucosa is hyperaemic. Most of the patients have been males below the age of 40, but no importance should be attached to this observation because of the very selective character of the material. The symptoms are those of lower urinary tract infection—frequency, dysuria, pain and haematuria. In our own case, dysuria was the pre-dominant symptom. The lesions respond to diathermy although more than one treatment may be needed. Disappearance of the lesions is accompanied by complete relief of the symptoms.

It is unfortunate that the term "nephrogenic adenoma" has been applied to this disorder. The resemblance of the histological appearances to renal tubules is admitted, and the potentialities of vesical mucosa in view of its embryological origin cannot be denied. It is clear, however, that we are dealing with an unusual response to infection on the part of the vesical mucosa. Clinical information relative to the cases reported by Friedman and Kuhlenbeck is often incomplete. In the better documented cases the relationship to infection is unmistakeable but it is of interest that in our own case the lesions appeared after the infection had been eradicated from the urinary tract. No specific organism has been implicated as the cause of this condition. There appears to be a latent period before the characteristic lesions appear. In Hasen's case this was as long as 6 years and in our own case the lesions did not appear until 14 months after the injury which was the starting point of the condition. Once begun, the condition seems to be progressive, fresh lesions forming until treatment is instituted. The symptoms of nephrogenic adenoma are those of an infective or inflammatory condition and not those of a tumour. The disease should be regarded, therefore, as a metaplastic change in the bladder mucosa in response to infection, but it must be agreed that the embryological derivation of the mucosa from mesoderm as well as entoderm may determine the peculiar nature of the changes. Perhaps "tubular metaplasia" would be a better title for the disorder.

In 2 of the reported cases there was an element of trauma as the patients sustained rupture of the bladder, and it is not impossible that our patient suffered a minor bladder injury. However, the evidence suggests that it was infection secondary to the rupture and its treatment that was the aetiological factor, rather than the injury itself.

Summary

We report an additional case of "nephrogenic adenoma" of the urinary bladder.

"Nephrogenic adenoma" is not a neoplastic condition but an unusual form of metaplasia of the vesical mucosa in response to infection.

The lesions respond well to treatment by diathermy.

Our thanks are due to Dr W. MacCullagh Wilson and Dr J. W. Black for the histological examinations and to Mrs J. Jenson for secretarial help.

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Nephrogenic Adenoma of the Urinary Bladder

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Nephrogenic adenoma is a rare benign tumour of the urinary bladder. It consists of raised, reddish, nodular areas separated by apparently normal epithelium. Histologically the tumour shows glandular spaces assuming a tubular pattern which are lined by a single layer of cuboidal or columnar epithelium. This tumour was first described by Davis (1949) who labelled it as a hamartoma. Friedman and Kuhlenbeck (1950) named it as "nephrogenic adenoma" depending upon its histological features. Hasen (1962) collected 11 cases from world literature and added 1 more case. Recently, Goldman (1972) has reported a series of 3 cases bringing the total number of reported cases to 15 only. One more case of nephrogenic adenoma is being presented in this communication.

Case Report

A 23-year-old Hindu male was admitted on 22nd January 1972 to the Urology Unit of Maulana Azad Medical College and Irwin Hospital with persistent severe haematuria of 7 days' duration. He gave history of intermittent haematuria, severe dysuria, and dribbling for the last 8 years. He had undergone suprapubic cystostomy and bladder neck resection for a suspected vesical calculus in 1963 but the dysuria and incontinence persisted. In 1966 a left nephrectomy had been performed elsewhere for left lumbar pain. He was investigated in this unit for dribbling and dysuria in December 1967, and was found to have a large vesical diverticulum, left ureteric reflux and chronic pyelonephritis. A diverticulectomy and left ureterectomy were performed on 19th January 1968. After operation the patient continued to have incontinence of urine, marked dysuria and intermittent haematuria. Repeated courses of antibiotics, urethral dilatations and imipramine were ineffective.

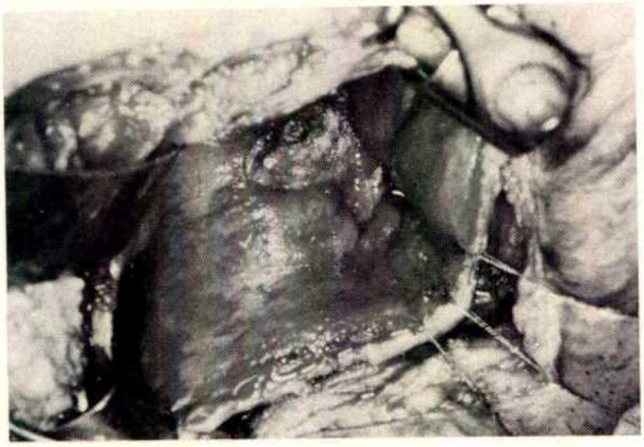

Fig. 1. Interior view of the bladder showing multiple small "tumours".

On admission cystoscopy revealed multiple papillary projections 2-5 mm in diameter situated over the trigone and posterior wall of the bladder with congestion of the intervening bladder mucosa. Neither ureteric orifice could be identified. The tumours were biopsied and fulgurated but transvesical excision had to be performed 1 week later for persisting haematuria. At exploration the lesion was found to be more extensive and diffuse (Fig. 1). The bladder was closed with catheter drainage. Postoperative progress was satisfactory except for a minor wound infection.

He was last seen on 26th July 1972. He still had dysuria and dribbling, but had been free from haematuria.

Histological examination of the tumours showed irregular focal ulceration of the urothelium (Fig. 2, A and B). The surviving epithelium had undergone basaloid hyperplasia at many places. The subepithelial lamina propria was markedly oedematous, and contained congested and dilated blood vessels and lymphoid aggregates with prominent germinal centres. A small number of plasma cells, lymphocytes and a few histiocytes were scattered throughout the lamina propria. An interesting feature of the biopsy was the presence of several small or large groups of tubular structures in the subepithelial connective tissue. Some of these tubular structures were cystically dilated. The lining epithelial cells were cuboidal, had a moderate amount of pale eosinophilic cytoplasm and vesicular round to oval nuclei. These tubules very much resembled the collecting tubules of the kidney.

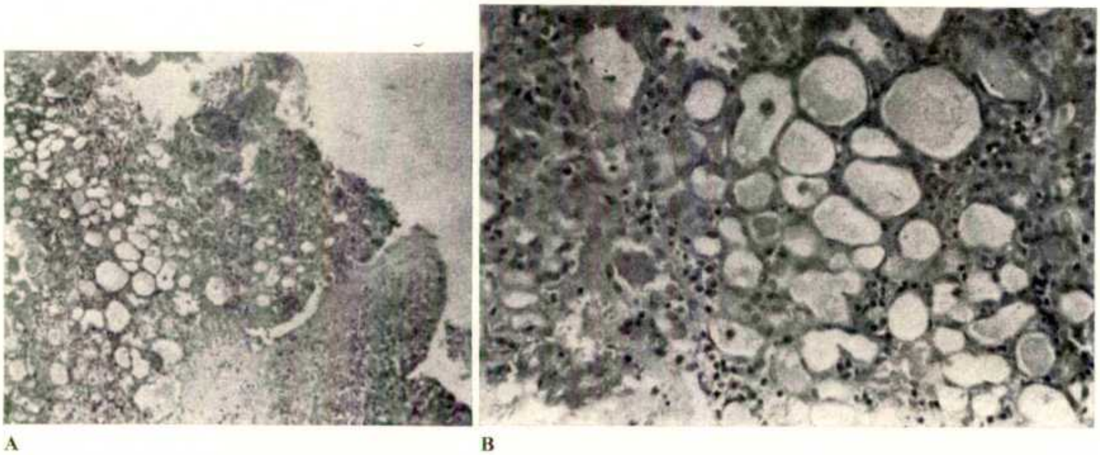

Fig. 2. A, Microphotograph under low power showing transitional epithelium in right lower quadrant and areas of tubular formation. B, High power showing tubular cystic spaces lined by cuboidal epithelium.

Comment

The origin of nephrogenic adenoma is not certain. Davis (1949) felt that chronic bacterial urinary tract infection played an important role in the recurrent and multiple nature of this hyperplastic lesion. He considered that glandular spaces were formed by invagination or plication of surface epithelium rather than from ectopic tissue in the bladder which gave rise to tubular or glandular structures. Friedman and Ash (1959) regarded this as a congenital lesion because the tumour was characterised by the formation of looped or convoluted tubules suggesting either mesonephric or metanephric pattern. Mostofi (1954) considered that this tumour was a manifestation of metaplastic behaviour of vesical epithelium. He advised that these cases should be closely watched for the development of cancer. Hasen (1962) agreed that the tumour arose as a result of metaplasia due to infection. The clinical presentation and prolonged history of chronic urinary tract infection in the present case would support the theory of metaplasia. Metaplasia of vesical epithelium may lead to the formation of a tubular pattern because of the dual origin of the vesical epithelium both from the entoderm as well as the mesoderm. The fact that endoscopic examination or cystostomy on 3 occasions in the past had not revealed any neoplastic projections, and the continuation of the recurrent cystitis over the years, support its aetiological role in the genesis of this tumour.

The condition seems to affect young males only. These patients present with gross haematuria associated with other urinary complaints due to urinary tract infection particularly dysuria. Haematuria varies from slight to profuse. Cystoscopy and biopsy usually confirms the diagnosis. As the tumours are small in size, cystography is not helpful in locating the lesions.

Transurethral resection or fulguration is the treatment of choice. But if this is not effective in controlling haematuria, transvesical excision and fulguration of tumour has to be carried out as the lesions are multiple and can be dealt with better by direct exploration and fulguration. These patients must be kept under observation as they are likely to develop recurrence of the lesions and haematuria for which repeated fulguration may be required. This would also exclude the development of malignant change.

Summary

A case of nephrogenic adenoma of the urinary bladder has been reported. This tumour is essentially benign and probably arises as a result of metaplasia due to chronic urinary tract infection.

The disease affects young males and is characterised by haematuria.

Fulguration of the tumour is effective in controlling haematuria.

A close watch and follow-up is essential to detect recurrence.

We are grateful to Dr R. K. Goel, Assistant Professor of Pathology, for his assistance in microphotographic work.

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Screening for Bacteriuria with a Dip-stick Test for Urinary Glucose

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The need for a simple yet reliable test to detect bacteriuria has been recognised for a long time, especially in epidemiological studies, to determine the incidence and distribution of asymptomatic urinary tract infection. However, the wide range of tests advocated (Simmons and Williams, 1962; *Lancet*, 1964; Sleigh, 1965) indicate that the ideal has not been found. A recent test is based on the detection of the small quantities of glucose normally present in urine. Morning urine usually has between 2 and 20 mg glucose per 100 ml and Scherstén and Fritz (1967) found that significant bacteriuria was associated with subnormal levels of glucose since bacteria in the bladder had metabolised the glucose. Subsequently a test paper was developed which was able to detect these small amounts of glucose. It consists of a lower ion-exchange portion which removes substances that may interfere with the test, and this is placed in the urine. The upper part of the paper contains an indicator system (glucose oxidase, peroxidase, O-tolidine) which changes colour to blue-green when the concentration of glucose is in excess of 1·5 to 2 mg per 100 ml. The test appeared successful in detecting bacteriuria in children and adolescent girls (Scherstén *et al.*, 1968) and this encouraged us to employ the test on urine samples from out-patients attending a hospital urological clinic for the first time.

Patients and Methods

New patients attending the urology clinic were sent a sterile universal container, with 0·5 gm boric acid added as preservative as advised by Porter and Brodie (1969). They were instructed to fast over night, to hold their urine in the bladder for a minimum of 6 hours and then to fill the bottle with a terminal-stream specimen of the first morning urine. At the clinic they were asked whether they had complied with the instructions and if not they were excluded from the trial. The urine specimen was then tested for small amounts of glucose with a commercially prepared strip, Uriglox, based on the paper described above, before it was sent to the laboratory along with a mid-stream specimen taken in the clinic.

A further group of first morning urine specimens were collected without special precautions from unselected patients in the urology wards. They were tested with Uriglox before being sent to the laboratory for examination. No preservative was added to these specimens. Where a patient had an indwelling catheter it was spigotted for 3 hours before taking the specimen.

In the laboratory all specimens were cultured by the dip-slide method using a commercial preparation, Uricult. The slides were coated with nutrient agar on one side and MacConkey agar on the other. Each specimen was also cultured by the semi-quantitative method in routine use. This employs a standard loop of 3 mm internal diameter and is similar to that described by McGeachie and Kennedy (1963).

To maintain consistent results the cultures were set up and read by the same observers, Uricult by J. D. S. and standard loop bacteriology by M. M. B. Neither knew the results of the Uriglox test. The results of culture were interpreted according to Table I.

Results

A total of 415 first morning specimens were collected from out-patients (Table II) and 39 were found to have significant bacteriuria, when examined by culture of a standard loopful. Only 23 of these urines (59%), however, gave a positive Uriglox test. Six false positive tests were recorded in the 368 specimens containing insignificant numbers of bacteria; all the specimens with bacteriuria of doubtful significance gave a negative test. The accuracy of the results was not influenced by the age or sex of the patient or the infecting organism.

Table I

Interpretation of the Results of Quantitative Urine Culture

Result of Urine Culture	Conclusion
Urines which gave no growth or yielded a mixed growth of contaminants at a concentration of up to 10^5 per ml	Insignificant bacteriuria
Urines containing coliform organisms at concentrations between 10^4 and 10^5 per ml either in pure culture or along with other organisms.	Bacteriuria of doubtful significance
Urines containing *Staphylococcus albus* in pure culture at a concentration of 10^5 per ml	
Urines containing urinary-tract pathogens at concentrations between 10^5 and 10^8 per ml	Significant bacteriuria

Table II

Results of Uriglox Test on Urine Specimens from Out-patients related to Culture of the Same Specimen

	Result of Culture			
	Significant Bacteriuria	Doubtful Bacteriuria	Insignificant Bacteriuria	
Uriglox Test:				
Positive	23	0	6	29
Negative	16	8	362	386
	39	8	368	415

When the Uriglox test was applied to 205 specimens from in-patients (Table III) a positive result was recorded in 35 out of the 62 urines (56%) with significant bacteriuria. In 4 of the instances where Uriglox failed to detect bacteriuria the causal organism was *Pseudomonas* *pyocyanea.* There were 10 false positive reactions and a negative test was again given by all specimens with bacteriuria of doubtful significance.

In all, 1,032 specimens were cultured by the dip-slide method and by standard-loop bacteriology. They comprised 415 first morning specimens preserved with boric acid from out-patients, a further 401 specimens from the same out-patients collected later in the day at the clinic and 216 specimens from in-patients. In 1,015 out of the 1,032 specimens (98%) the results of the 2 cultural methods agreed (Table IV). Results from 12 specimens differed only in that one method indicated a growth of doubtful significance whereas the other a significant or alternatively an insignificant growth of the same organism. In 5 specimens, however, there was complete disagreement. This could not be explained in 3 of the specimens, but was due in the other 2 to the media on the dip-slide failing to support the growth of staphylococci on 1 occasion and coliform organisms on the other. In 4 other instances enterococci did not grow on the MacConkey-medium side of the dip-slide although they were present in significant numbers on the side coated with nutrient agar.

Table III

Results of Uriglox Test on Urine Specimens from In-patients related to Culture of the Same Specimen

	Result of Culture			
	Significant Bacteriuria	Doubtful Bacteriuria	Insignificant Bacteriuria	
Uriglox Test:				
Positive	35	0	10	45
Negative	27	9	124	160
	62	9	134	205

Table IV

Comparison of Dip-slide and Standard-loop Methods of Urine Culture

Results of Cultural Methods	Number of Specimens Examined		
	From Out-patients	From In-patients	
In agreement	805	210	1,015
In disagreement	11	6	17
	816	216	1,032

When the results of culture of the first morning urines from the out-patients were compared with the specimens collected from these same patients when they attended the clinic later in the day, they were found to be in very close agreement.

Discussion

The 2 main objects of this investigation were to determine the value of Uriglox as a spot test for bacteriuria in patients attending a urological department and to compare Uricult, a dip-slide method of urine culture, with the standard-loop technique in routine laboratory use.

In order to keep instructions reasonably simple, out-patients were asked to collect a terminal stream urine specimen without any particular precautions to prevent contamination. Such specimens were considered by Linton and Gillespie (1969) to be acceptable for bacteriological examination. It was made clear, however, that the urine had to be a first morning specimen voided after a period of overnight fasting. For the Uriglox test the urine must remain in the bladder long enough for the glucose to be metabolised by multiplying bacteria and a period of 6 hours is recommended. It is also necessary that the patients do not eat or drink during this period since fluid intake may lower and ingestion of food may raise the content of glucose normally found in the urine.

Boric acid was added to the universal containers issued to the out-patients to prevent the multiplication of bacteria in transit as recommended by Porter and Brodie (1969). We found this did not interfere with subsequent culture as there was little difference between results obtained from the early morning urines as compared with those from specimens voided at the clinic. Furthermore, at the recommended concentration we found that boric acid did not interfere with the Uriglox test. However, until we warned patients that the specimen jar sent to them contained a preservative several tipped or washed out the boric acid crystals; these patients were excluded from the trial.

In previous studies Scherstén *et al.* (1968), Paterson (1972) and Emmerson (1972) have found Uriglox an accurate detector of bacteriuria in children and ante-natal patients. Emmerson (1972), however, stressed that the test should only be used in early pregnancy when urinary glucose levels are still normal in healthy patients. In contrast to these trials most of our patients complained of symptoms referable to the urinary tract. Our results were disappointing but we believe that the poor ability of this test to recognise bacteriuria may have been due to failure of these patients to comply with the regulations concerning urine collection despite their claims to the contrary. Many of our patients had been plagued with their symptoms for years and consequently may no longer have regarded them seriously.

Uriglox will not detect bacteriuria if the fasting urine is likely to contain excessive amounts of glucose (as in diabetes) or if the bacteriuria is due to an organism which fails to metabolise glucose actively (such as *Pseudomonas pyocyanea*). None of our out-patients, however, was known to be a diabetic and in no case was the infecting organism *Pseudomonas pyocyanea*.

The results obtained with Uricult in urine specimens from in-patients were not inferior to those from the out-patients despite the fact that the specimens were collected without strict precautions and that the patients included some receiving intravenous infusions of glucose and others with catheters and ileal conduits all of which could interfere with the test. We believe that this finding supports our suggestion that inadequate care in collecting the samples was the cause of the test giving such poor results in the specimens from out-patients and it does not matter if this was due to inability or unwillingness on the part of the patients to fulfil the requirements of the test. Knox (1972) has similarly found the test of limited value in general practice.

We endorse the opinion of Guttmann and Naylor (1967), Arneil, McAllister and Kay (1970) and Jackaman, Darrell and Shackman (1973) that Uricult is a simple and reliable method of quantitative urine culture and there were only a few discrepancies between this method and culture with a standard loop. Some of the differences were due to failure of the medium on the dip-slide to support bacterial growth, a deficiency previously commented on by Maskell and Polak (1970). Uricult, however, since it is a method of bacterial culture, requires facilities for incubation of the slides and some skill on the part of the observer who subsequently reads the results. Uriglox on the other hand is a very simple test which can be read within 10 minutes, and since it depends on a colour change the result is very easy to interpret. It is, therefore, disappointing that we did not find Uriglox a reliable test, and whatever the explanation of our results we cannot recommend this screening test for use in patients attending a urological out-patient clinic.

Summary

Uriglox, a dip-stick screening test for bacteriuria, and Uricult, a dip-slide method of culture, were compared with semi-quantitative culture by a standard technique.

The dip-stick test, carried out on 415 specimens of urine from out-patients and 205 from in-patients, gave negative results in over 40% of specimens shown to have bacteriuria on culture.

The results of the 2 cultural methods were in close agreement.

We wish to thank Mr A. G. Graham and Mr K. F. Kyle for allowing us to study their patients.

The Uriglox test strips were kindly provided by William R. Warner and Co. Ltd, and part of the cost of the Uricult dip-slides was met by Bristol Laboratories, Ltd.

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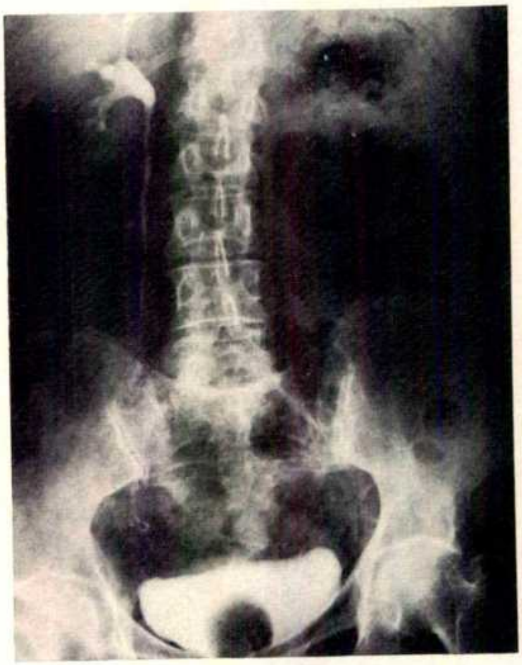
Short Case Report

Renal Emphysema

A case of gas formation in the kidney is described:

An elderly diabetic lady was admitted with uncontrolled diabetes and a mass in the left loin. Intravenous urography (Fig.) showed the left kidney to be non-functioning, with gas in the perinephric space, kidney substance and collecting system. At operation, the kidney was oedematous and haemorrhagic. A left nephrectomy was carried out. On cutting the kidney small bubbles of gas were found scattered throughout the parenchyma. She made a good recovery, her diabetes rapidly coming under control. Three months later she died from a similar infection in remaining right kidney.



35 previous cases of gas formation in the urinary tract as a result of carbohydrate fermentation by aerobic organisms have been described (Costas, 1972; Mosley, 1973). All such cases are associated with obstructive uropathy, diabetes, or both, this last group having a mortality rate of 70%. Surgical intervention appears to offer the best hope of survival.

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Book Reviews

Cystourethrography—A Radiographic Atlas. By MARJORIE HERTZ, pp. 280, with 237 illustrations. Amsterdam: North Holland, 1973.

The main part of this book is a presentation of radiographs, with short case histories as captions. The author has collected examples of most of the common conditions likely to be encountered at cystourethrography, as well as many rarities. The quality of reproduction of the radiographs is excellent and almost without exception, the features referred to in the text are demonstrated clearly.

The book could have been improved by using fewer radiographs for each case. These are often repetitive or show no abnormality. One result of having so many illustrations is that the text is frequently widely separated from them, so that it is impossible to read the book without having constantly to refer backwards or forwards to find the appropriate picture.

Not everybody would agree with the suggestions that cystography in males may need a 60% concentration of Hypaque or that girls should be examined standing. There are few instances in which a 15% concentration of Hypaque does not produce satisfactory contrast and most girls find it easier to micturate sitting than standing. However, there is little else that might be controversial in this book and the text is clear and concise with numerous useful references.

As an atlas of radiographs this book will be extremely useful for anyone wishing to familiarise himself with the range of abnormalities which may be encountered on cystography. Many will find it of more value as an up-to-date compendium of references to recent publications. It is highly recommended for anyone needing either kind of information.

W. S.

Organ Preservation. By DAVID E. PEGG. Pp. xiv+286 with illustrations. Edinburgh: Churchill Livingstone. 1973. £5·00.

The publication of symposia is not always justified but this collection of 22 papers and discussion presented at Northwick Park Hospital in November 1972 is a valuable exception. This is a topical subject but real progress is often difficult to detect because of the fashions and vested interests in machines and solutions. This book reveals the considerable gap between clinical practice and experimental data, and for this reason can be highly recommended to all those concerned with the problems of organ preservation.

G. D. C.

Developmental Nephrology. By WALLACE W. MCCRORY. Pp. xii+216. Cambridge, Mass.: Harvard University Press. 1972. £8·20

"The embryologic development of the human kidney can be viewed as a goal orientated program aimed at achievement of the unique anatomic configuration responsible for the aggregate functional efficiency of its 1,000,000 nephrons." In the opening sentence Professor McCrory outlines the subject-matter of his monograph and at the same time reveals a certain pomposity of style which is irritating in some of the more speculative passages.

The first chapter outlines the embryological development of the kidney, illustrated by some beautiful microdissections by Dr Jean Oliver. Subsequent chapters deal with the development of renal function *in utero*, quantitative measurement of renal function during growth in infancy and childhood, renal function in the post-natal period and the cellular processes underlying growth and development of the kidney. There are 20 pages of references.

Professor McCrory has performed a most useful function in collecting data from separate disciplines for his monograph, and it will be of interest to urologists, particularly those concerned with the care of children. It serves to emphasise that some of the most important events in the development of the kidneys occur in the first few months after birth, and that future developments in paediatric urology must be directed towards very early diagnosis and treatment to permit optimal conditions for renal growth.

T. M. B.

The Tailored Urogram. By ANTHONY F. LALLI. 1st Edition. Pp. xi+253 with 309 illustrations. Chicago: Year Book Medical Publishers, Inc. 1973. £9·75.

The author states that his aim was a simple, clearly non-exhaustive—albeit pleasant—way of learning how to perform urograms and how to begin the interpretation of them. The first chapter deals with the technical aspects. It includes preparation of the patient, contrast medium dosage and reactions, and some useful comments on the information to be derived from the preliminary film with notes on the nephrogram and ureteral peristalsis. The technique of a routine I.V.P. is described after which the approach to specific problems such as hypertension, stasis and ureteral colic is discussed. The author stresses the importance of tailoring the examination to the patient's needs; the emphasis is on an intelligent use of radiographic techniques to produce the maximum information on each radiograph taken. In the four remaining chapters pathology is considered from a radiologist's standpoint. Four major radiological abnormalities are taken and the relevant pathology discussed in an easy style drawing on the author's wealth of practical experience. Suggested methods for the beginner to use in different situations with appropriate differential diagnoses are outlined in an appendix.

This is a very readable book and provides a considerable amount of practical information not found in the standard text books. It should be of considerable help to trainee urologists as well as radiologists. Numerous radiographs of adequate quality are included.

S. M. H.

Books Received

The Life of Hamilton Bailey. By S. V. HUMPHRIES. Beckenham, Kent: Ravenswood Publications, 1973. £3.

Recent Advances in Surgery, No. 8. By S. TAYLOR. Edinburgh: Churchill Livingstone. 1973. £5·50.

ABSTRACTS OF THE PROCEEDINGS OF THE UROLOGICAL SOCIETY OF AUSTRALASIA

26th ANNUAL GENERAL MEETING, WELLINGTON, NEW ZEALAND, 1973

President: H. W. Gowland (Wellington)
Honorary Secretary: H. Thomas (Sydney)
Editor: G. F. Murnaghan (Sydney)

The Uretero-vesical Junction Physiopathology

By W. Gregoir

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The musculature of the uretero-vesical junction is constituted of muscular bundles which are not strictly longitudinal but slightly oblique. At the level of the submucosal ureter and the meatus, decussations and arciform muscle fibres are found. The juxtavesical ureter is surrounded by a supplementary musculature which is also longitudinal or slightly oblique; it appears very early in the embryo and is of endodermic or vesical origin. The innervation of the uretero-vesical junction is of a mixed type, sympathetic and parasympathetic. Nervous ganglia contain parasympathetic cells as well as sympathetic neurones; isolated nerve cells occur in the ureteral wall and are sympathetic as well as parasympathetic as can be proved by histochemistry; the staining of acetylcholine-esterase is characteristic of the parasympathetic cells being evidenced by fluorescence methods.

Prevention of reflux in a normal ureter cannot be explained either by the classic "passive valve theory" or by the more recent "active muscular theory". Many contradictions are to be found against either theory by very simple observations: the absence of reflux in the cadaver or in the foetus when the muscle fibres are not yet differentiated is against the muscular theory, as well as the fact that in some cases of congenital reflux, musculature of the lower end may be hypertrophied instead of insufficient; the frequent absence of reflux after meatotomy and the absence of reflux in a normal newborn or foetus, when the submucosal segment is still very short, are against the passive theory. The supporting tissues, collagenous and elastic play a very important role in the physiopathology of the uretero-vesical junction. Absence of reflux can only be explained if one considers the conjugate action both of the musculature and the supporting tissues. The arrangement of the muscular fibres as well as that of the elastic and collagenous fibres is like the meshes of a net; the more the intravesical segment is stretched out the tighter it gets.

Insufficiency of either muscular or supporting tissue will be responsible for primary reflux. On the other hand any condensation or loss of extensibility will explain the development of a primary megaloureter; the most frequent tissue malformations encountered are—collagenous condensation with muscular scarcity giving rise to achalasia, epithelial dysembryoplasia, muscular hypertrophy or dysplasia. Recent studies have shown that in some cases where the explanation of a primary megalo-ureter was difficult by classic histology, the electron microscope would demonstrate gross cellular abnormalities.

Hiatal hernia should not be confounded with a bladder diverticulum where the ureter implants; it is secondary to a malformation of the ureterovesical hiatus which is congenitally too large; the hernia develops inside of the ureteral sheath and it is accompanied usually either by reflux or by some degree of functional obstruction.

The normotopic ureterocele is secondary to a primary hypertrophy of the meatal musculature; the obstruction is due to a marked hypertrophy of the meatal muscle and the dilatation develops just above, that is in the submucosal segment. As for the ectopic ureterocele, the obstructive factor is less evident; in some cases there is a complete lack of musculature in the last millimetres above the meatus; in some other cases the obstructive factor seems to be a compression of the intra-urethral segment by the bladder neck musculature.

Some views on the mechanism of acquired obstruction are to be reviewed. For example, dilatation of the upper urinary tract in prostatic adenoma is not secondary to a compression of the intramural segment by the adenoma itself but to a stricture or a strangulation of the intravesical segment by a strongly hypertrophied and generally infiltrated bladder wall.

Also, in female genital prolapse, ureteral obstruction is not due to compression by the uterine artery but to a sharp angulation at the level where the ureter penetrates into the bladder wall.

Electromanometry in Normal and Reflux Ureters

By D. Lenaghan, MS, FRCS, FRACS

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Intraluminal pressures were recorded in the ureters of 22 dogs and 50 paediatric patients, 7 of whom had normal urinary tracts, 14 had vesico-ureteral reflux, and 29 had other conditions.

Ureteric resting pressure was usually low, varying from 0 to 10 mm Hg. The pressure in the lower third of the ureter was higher than elsewhere. Ureteric resting pressure was usually less than bladder pressure. The pressure in the lower ureter varied rapidly with that of the bladder suggesting a reflex connection. When lower ureteric pressure was between 35 and 40 mm Hg (usually bladder pressure was then about 50 mm Hg) peristalsis was not seen in the lower ureter though it persisted in the upper and middle portions of ureter where the resting pressure was not as high. Rarely, the response to altered bladder pressure was a change not in pressure in the ureter but in frequency and amplitude of the ureteric waves. The amplitude of the peristaltic waves was highest in the middle and lower ureter.

Peristaltic waves commenced in the pelvis and traversed the whole ureter at a speed of 3 to 6 cm/sec and at rates of 6 to 30 per minute. The peristaltic wave traversed a short polythene bridge in a divided ureter but was not propagated in an empty ureter.

In the reflux ureter low-amplitude intramural waves were absent. In comparison with the contralateral side, reflux ureters often showed less frequent peristalsis, lower amplitude waves, and higher resting pressures.

Reflux was induced experimentally in the dog. Two catheters were inserted into the ureter through the renal parenchyma, one located in the upper ureter and one in the lower. It was found that reflux into the lower ureter occurred more readily and at lower bladder pressures than into the upper ureter. When reflux took place, abolition of peristalsis followed. It was absent for only a couple of minutes in the upper ureter, but in the lower ureter it remained absent for several minutes.

Rapid return of peristalsis in the upper ureter renders reflux alone harmless to the kidney. Prolonged peristalsis in the lower ureter is consistent with the observation that reflux is often confined to this segment, and is suggested as an explanation for dilatation of this segment in certain examples of reflux.

Muscle Cell Dimensions and Population in Mega-ureter in Children

By F. Douglas Stephens, DSO, MS, FRACS

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In this Department studies of 300 mega-ureters have been carried out by Dr Leo J. Cussen with correlation of the muscle cell hypertrophy and hyperplasia with the nature of the dilatation. After exclusion of mega-ureter associated with myelomeningocoele deformity the dilated ureters were classified into 4 groups—obstructive (201), reflux (75), idiopathic (18) and Triad Syndrome ureters (6)—each with distinctive muscle cell pattern.

In each specimen of ureter the area of muscle and the number of nuclei in a transverse section of 19 μ thickness were estimated, using a graduated grating on the ocular of a microscope and from these data the cell size and numbers were estimated.

Hypertrophy

Dilated ureters with identifiable intrinsic obstruction showed moderate hypertrophy up to 2 to 3 times normal average dimensions, whilst those which showed enlargement secondary to urethral obstruction showed more hypertrophy at 3 to 5 times normal.

Reflux evoked minimal hypertrophy (within the normal range) when it occurred either as vesicoureteral reflux (72 specimens) or ureter to ureter (3 specimens). The so-called idiopathic mega-ureters and the few Triad ureters showed no hypertrophy of muscle.

Hyperplasia

Intrinsic obstructions caused moderate hyperplasia of up to 3 to 5 times normal, whilst urethral obstruction caused gross hyperplasia up to 5 to 50 times normal. Reflux showed only minimal hyperplasia of 1 to 3 times the normal numbers. The idiopathic mega-ureter exhibited no hyperplasia and the Triad ureter showed absence or clumping of muscle or hyperplastic disorganised masses.

Experimental Obstruction and Reflux. Cussen applied the same cell measuring techniques to test the reaction of adult canine muscle cells to chronic urethral obstruction with reflux. Degrees of hypertrophy and hyperplasia in chronic obstruction and reflux were similar to those in human ureters. Urethral obstruction, however, evoked a reaction similar to ureteral obstruction but not to the gross degree which had been noted in the human ureters.

Estimation of muscle cell size and numbers has aided the pathological classification of mega-ureters; with the greater accuracy afforded by these criteria, the diagnosis of neuromuscular incoordination has been eliminated and simple overgrowth of developmental origin has been established as an entity in its own right.

Classification of mega-ureters is proposed as follows:

(*a*) Acquired megaureter due to pre- and postnatal obstruction with hypertrophy and hyperplasia. Obstruction may be due to atresia, stenosis or commonly to valve formation in the ureter. All types occur in the upper, middle or lower parts of the ureter but valve most commonly occurs at the distal end of the ureter.

(*b*) Developmental mega-ureter due to overexpansion of the ureteric bud with no hypertrophy beyond the normal range of cell size and occurring as non-reflux (idiopathic) and reflux subtypes, with mild hyperplasia commensurate with slight increase in work load, and with a Triad subtype without any set pattern of size or structure.

Surgical Reconstruction of Mega-ureter

By Dennis Arnold, FRCS, FRACS

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and Royal Prince Alfred Hospital, Sydney, N.S.W.

In the past, simple reimplantation of obstructive mega-ureter tended to be followed by the new development of reflux while surgical procedures which corrected reflux in the mega-ureter tended to lead to fixed dilatation and stasis. However, new reconstructive procedures such as described by Hendren (1969) now offer a great improvement in outlook.

In this series there were 30 tailoring procedures carried out in 23 patients. Seven patients had simultaneous bilateral operations while 4 patients had the ureters of their solitary kidneys tailored. In 12 patients only 1 ureter was tailored: in the refluxing cases in this group, bilateral reflux surgery was carried out in 7 of the 8 patients.

Most of the patients were between the ages of 1 and 10 years but the youngest was 6 months and oldest 20 years of age. The first operation in this series was done in August 1969 and the last in October 1972. A further 15 ureters have been tailored but the operations are too recent for evaluation and they have not been included in this report.

The operative technique generally followed the description by Hendren (1969), although the tailoring of the lower ureter was more extensive and usually extended to a point above the brim of the pelvis; at times the medial rather than the lateral aspect of the ureter was removed, depending on the disposition of the blood supply.

There were no deaths and no patient required subsequent ureteric catheterisation, nephrostomy, nephrectomy or urinary diversion. Three patients needed postoperative urethral catheterisation to induce healing of bladder fistulae. So far only one ureter has subsequently been tailored in its proximal part through a loin incision and only a few of the others seem likely to need this procedure.

The obstructive group was made up of 13 ureters in 10 patients, all boys between the ages of 6 months and 9 years. In one bilateral and one solitary case the dilatation has persisted. Each of these 2 patients had had 2 previous operations to the lower urinary tract and it now seems likely that they have some disturbance of the nerve supply to their bladders. The remaining 8 patients (11 ureters) are free of infection, as they were before operation and their intravenous pyelograms indicate a lessening of stasis in the reconstructed ureters. Postoperative cystograms have not been carried out.

In the refluxing group there were 17 ureters in 13 patients, 7 males and 6 females between the ages of 8 months and 20 years. Each patient in this group had a history or evidence of recurrent urinary infection, much more marked in the girls; varying degrees of renal damage were evident on X-ray examination, generally tending to be more advanced in the older patients. Of this group of 13, 2 patients still need continuous suppressive anti-microbial chemotherapy to keep their urines clear—one is a "unilateral" case whose contralateral refluxing upper tract has no effective function and is to be removed at a later date; the other is a girl with a solitary kidney whose ureter has been operated upon twice before and who probably has a neurogenic disturbance of bladder function. The remaining 11 patients (15 ureters) are all free of infection and require no chemotherapy. In none of the 11 has there been any increase in upper tract dilatation. One patient will need a pyeloplasty for pelvi-ureteric junction obstruction which was present before the tailoring procedure was carried out.

The tailoring procedure is time-consuming and requires meticulous technique. The initial encouraging postoperative findings in the present series suggest that the tailoring procedure for mega-ureter may come to be regarded in much the same way as pyeloplasty is for hydronephrosis due to pelvi-ureteric junction obstruction. It is to be hoped that the long linear scars in these reconstructed ureters will not cause trouble when the smaller children grow. In the short term the tailoring operation appears to be safe, effective and worth while. In the long term there may be troubles but these are unlikely to be worse than those occurring spontaneously in patients denied operation.

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Ureterostomy *in situ*

By R. R. A. SYME, FRCS, FRACS

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The procedure of ureterostomy *in situ* with placement of a catheter into the ureter for drainage purposes without mobilisation of the ureter, is an alternative to nephrostomy which may be used to relieve acute anuria or as an adjunct to conservative surgical procedures in the upper urinary tract. It may be advantageous over nephrostomy because it is extremely easy and quick to perform, it requires no positional change of the patient during surgery, it can be carried out under light, general or local anaesthesia, it entails minimal tissue damage without haemorrhage or renal damage and the catheter does not become displaced and may be easily managed in the right iliac fossa location and can be changed easily.

The risk of development of ureteric stricture, inadequate drainage or inadvertent location below the proximal point of obstruction have caused anxiety but are theoretical disadvantages. In practice, ureteric stricture has not developed provided small calibre catheters have been used in the range of 10 French gauge or even smaller with plastic tubes. Drainage has been adequate provided that the catheter tip is located within the renal pelvis; blockage of the catheter has rarely occurred and it has been proved possible to manage inspissated pyonephrosis by the addition of suction drainage. It is essential that the most proximal point of the obstruction be accurately defined. In patients requiring long-term drainage easy catheter change requires that the catheter be brought to the surface in a smooth arc.

Indications for Surgical Treatment of Primary Vesico-ureteric Reflux

By G. F. MURNAGHAN, MD, CHM, FRCS

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The features of primary vesico-ureteric reflux have been analysed in a series of 98 female patients in respect of age at the time of study, the length of the intravesical segment of ureter of the incompetent orifice, the extent of the reflux, the ureteric response to reflux and the presence and severity of any radiological evidence of chronic pyelonephritis.

The analysis strongly suggested that an intravesical segment length of 10 mm might be critical to the prevention of reflux in most patients and at any age. In the separate age-groups the distribution of the intravesical length showed that the incompetent orifice had a longer intravesical segment as the series progressed through childhood towards adult life, it was strongly suggested that any patient who emerged from childhood into adult life with persistent reflux through an immature junction with an intravesical length of less than 10 mm would almost certainly have radiological evidence of chronic pyelonephritis.

When reflux was confined to the lower spindle of a normal calibre ureter the incidence of radiological evidence of pyelonephritis was 37% but the age scatter suggested that this grade 1 reflux might commonly disappear spontaneously.

When the reflux outlined the entire ureter and collecting system but without dilatation the incidence of pyelonephritis remained the same (35%) with a suggestion that this grade 2 reflux was more slow to mature the orifice and spontaneously regress.

When the reflux was accompanied by mild or moderate dilatation of the ureter and collecting system, the incidence of chronic pyelonephritis rose to 70% and many of these patients presented in middle age. This grade 3 reflux was invariably associated with pyelonephritic disease after the age of 16 years and did not usually occur through incompetence of junctions with intravesical segments longer than 10 mm.

When reflux was associated with gross dilatation of the ureter and collecting system (grade 4) then the incidence of chronic pyelonephritis rose to 89% and usually presented in early life with gross renal damage.

The analysis indicated that the extent of the mechanical deficiency of the uretero-vesical junction and the presence of dilatation in the ureter at the time of reflux correlated with the extent of renal damage when taken in respect of age.

From these considerations there emerged some specific suggestions for more particular indications for surgical correction of primary reflux. Anticipation that the incompetent junction might mature towards normal adult proportions would justify an expectant programme of treatment of primary reflux with anti-bacterial drugs, with or without urethral instrumentation in all patients with grade 1 reflux and in many patients with grade 2 reflux. If this conservative programme fails to control urinary tract infection then surgical correction of primary reflux should be recommended. Surgical treatment would also be required if the measured deficiency of the intravesical segment of the ureter in respect of age is so marked that maturation might be impossible or remote in time. In most patients with such deficiency of the uretero-vesical junctions the reflux would be voluminous and total in extent with ureteric dilatation to indicate some degree of ureteric strain. Surgical correction of such grade 3 reflux would be appropriate as a preventive measure against the almost certain development of chronic pyelonephritis and regardless of symptoms or association with infection. Surgical correction of grade 4 reflux, sometimes requiring extensive surgery, would clearly be indicated in early life.

Treatment in Vesico-ureteric Reflux

By W. L. F. UTLEY, FRACS

Christchurch, New Zealand

It is considered that infants with mild or moderate vesico-ureteric reflux do not develop progressive renal damage; surgical correction of the reflux is therefore not indicated in such cases who may be managed conservatively with careful control of their urinary tract infection as carried out in other children without vesico-ureteric reflux.

In the infant with gross vesico-ureteric reflux progressive renal damage will occur and may be life-threatening if the reflux is bilateral; in such patients surgical correction of the reflux is required. In order to prevent early death if the reflux remains gross and bilateral or to prevent serious renal damage despite regression of the reflux from gross to moderate degree and in order to prevent renal damage and allow the kidney to grow at a normal rate then surgery must be performed at a very early age.

It is possible that some renal damage may be sustained during intra-uterine life and cannot be prevented at this time. However, if the reflux is diagnosed as soon as possible after birth and early surgical correction is performed to arrest gross reflux then it is considered that the number of young adults presenting with chronic renal failure will be lessened.

Vesico-ureteric Reflux after Renal Transplantation

By D. URQUHART-HAY, FRCS, FRACS,
J. MCILWAINE, FRCS, FRACS,
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Techniques of implanting the ureter in renal homotransplantation are varied. Avoidance of stricture, ureteric necrosis and fistula formation is important as is the prevention of vesico-ureteric reflux which is well known to be associated with persistent urinary infection after renal transplantation.

In the Wellington Hospital a method has been used in which the ureter is passed through an oblique tunnel in the bladder wall and a nipple created on its end. This method has been applied in 49 patients receiving cadaveric renal homografts, 20 of whom have subsequently been investigated radiologically for evidence of vesico-ureteric reflux and/or stricture formation.

The method used was described by David Innes Williams for the reimplantation of ureters in children with vesico-ureteric reflux (Williams and Eckstein, 1965).

The bladder is opened in the midline anteriorly. The appropriate side of the bladder wall is grasped with the left hand and using a pair of McIndoe dissecting scissors a small hole is made through the lateral muscular wall of the bladder slightly obliquely, at a point about 4 cm above and lateral to the appropriate ureteric orifice. The points of the scissors will be visible beneath the mucosa on the inside of the bladder and may be advanced under vision, using small snipping movements, down the submucosal plane for a distance of 2 to 3 cm and thrust through the mucosa into the bladder interior in the vicinity of the patient's ureteric orifice. An oblique muscular and submucosal tunnel some 2 to 3 cm is thus created. A 20 to 25 cm length of rubber tubing (size 10Ch) is pushed on to the points of the scissors and guided through the tunnel as the scissors are withdrawn. The ureter is now loosely sutured to the end of the tubing and "railroaded" through the tunnel and into the bladder. A nipple is created by seizing the mucosa of the ureter with haemostats some 1 to 1·5 cm within its lumen and everting the mucosa. Four sutures of 0000 chromic catgut are used to anchor the nipple to the bladder mucosa, making sure that the sutures include the adventitial coat of the ureter as well as its free margin to maintain the cuff. Ureteric splintage is not necessary but was occasionally used to measure urine flow from the grafted kidney; in such cases a plastic tube (9Ch) was inserted and anchored at the nipple with a 000 catgut suture.

In the group of 20 patients in whom micturating cysto-urethrography was done within 4 to 42 months after transplantation, vesico-ureteric reflux occurred in only 1 case.

Intravenous pyelography revealed no evidence of hydronephrosis in any of the patients, although in one there was slight fullness of the lower 7 cm of the ureter and in another slight fullness throughout the entire length of the ureter. In 1 patient there was a small diverticulum adjacent to the site of implantation of the ureter and in a second patient there was a similar diverticulum related to the incision in the anterior bladder wall.

Historically, ureteric implantation has been made by creating either an oblique submucosal tunnel or a terminal cuff. The former method is superior in that it endures longer and resembles more closely the normal uretero-vesical valve. The nipple method in which the end of the ureter is rolled back to form a cuff, when used above has given equivocal results in preventing reflux (Hill, Dodson and Hooper, 1955; Grey, Flynn and Goodwin, 1957). This may be because of a gradual disappearance of the nipple, insufficient length of nipple or insufficient anchoring of the nipple.

The ureter of the cadaveric renal homograft is usually of normal calibre, straight and elastic, and provided its blood supply is adequate should, on the basis of past experience, be easily successfully implanted. By passing it obliquely through the bladder wall in the submucosa between mucosa and muscularis to reach its orifice at the lateral wall of the trigone a valvular effect is obtained. The ratio of length of intramural ureter to diameter of ureteric orifice should be 5 to 1, which means a submucosal tunnel length of 2 to 3 cm. A mucosal cuff which reduces the risk of stenosis may well contribute to reflux prevention provided it is firmly anchored and does not withdraw and become flush with the surface.

In this series in which three surgeons have carried out the procedure, the tunnel and cuff method has been found effective in the prevention of vesico-ureteric reflux in cadaveric renal homografts.

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Natural History of Reflux and Long-term Effects of Reflux on the Kidney

By D. LENAGHAN, MS, FRCS, FRACS

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At Royal Children's Hospital, Melbourne, vesico-ureteral reflux was treated medically with multiple micturition and antibiotics during the period 1953-1970. There were 102 patients with reflux unaccompanied by any other urological abnormality with adequate data for retrospective study. The duration of follow-up was not less than 5 years and in some patients was 18 years.

There were 35 males and 67 females with a total number of 167 ureters exhibiting reflux. Reflux was bilateral in 80% of the males and 55% of the females. Most of the males presented during the first year of life and 80% of them had presented by the age of 3 years. Only 24% of the females had presented at that age and their peak age of presentation was 7 years. Urinary tract infection was the most common mode of presentation and was seen in nearly 75% of males and over 90% of females.

Of the 167 refluxing ureters, 83 underwent cessation during the observation period. In normal calibre ureters (those up to 1 cm in diameter on X-ray during reflux) the incidence of cessation was 66%. In moderately dilated ureters (1 to 2 cm diameter) there was cessation in 33%, while in grossly dilated ureters (larger than 2 cm diameter) the incidence of cessation was only 14%. There was no tendency for normal ureters to become dilated as a result of prolonged reflux. In dilated ureters about 25% ceased reflux, 25% reverted to normal calibre during growth though continuing to exhibit reflux, and 50% remained with both dilatation and reflux.

43 of 102 patients lost reflux and in the main these had either unilateral reflux or normal calibre ureters. Reflux found in infancy often ceased in childhood but otherwise cessation was more common after 14 years of age.

Radiography of the kidneys defined growth changes, scarring and calyceal abnormalities. The development of renal lesions was more common when reflux persisted and when the kidneys were radiologically abnormal at the start of follow-up. Normal kidneys deteriorated only when reflux was prolonged in duration, bilateral and in the presence of dilated ureters.

Urinary infections after diagnosis were more common in females, more common during the first 5 years after diagnosis, and uncommon after reflux had ceased.

Kidney deteriorations were more common when urinary infections were recorded especially in females.

Conservative management of reflux is urged during the first 5 years of life if possible. Anti-reflux surgery is indicated in bilateral reflux especially when associated with dilatation of the ureters, in the presence of abnormal renal parenchyma and in females in whom it is likely to persist into adult life.

The Ovarian Vein Syndrome

By DAVID E. YOFFA, FRACS

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The ovarian vein can be the cause of chronic pain in the loin. Cases curable by ovarian vein ligation are diagnosed from the characteristic symptoms usually associated with radiological evidence of ureteric dysfunction.

J. Craig Clark described the ovarian vein syndrome in Emmett's text book of *Clinical Urography* (second edition 1964). He attributed the right ureteral obstruction at the level of S.1 or approximately 14 cm from the uretero-vesical junction to an aberrant ovarian vein.

A personal series of 10 operated cases is described; the findings and conclusions, in many respects, differ from those previously reported.

8 of the 10 cases have been right sided. At presentation the age of the patients varied from 21 to 56 years; 4 of the patients were aged 29 years and 3 were 36 years old. The symptoms comprised chronic dull loin and lower abdominal pain, usually increasing in severity during the day and with work. The onset of symptoms was often related to a particular pregnancy or aggravated by further pregnancies. There was no evidence of urinary infection in these patients.

The diagnosis should be suspected from the combination of characteristic symptoms, usually associated with pyelographic changes comprising the irregularity, kinking and dilatation of the upper ureter. Mild pyelocaliectasis may be present and delayed emptying of the renal pelvis can sometimes be demonstrated during pyelography with induced diuresis. Retrocaval ureter and vesico-ureteric reflux must be excluded.

Pathogenesis of the syndrome can be explained by the following considerations.

(i) The ovarian vein(s) dramatically increase(s) in size during pregnancy and in many cases may develop incompetence of the upper venous valve which may remain incompetent post-partum.

(ii) The subsequent increased venous pressure in the ovarian vein, particularly on the right side where the vein(s) empties into and has connections with the inferior vena cava may result in pain similar to that associated with peripheral varicose veins.

At operation the thickened and dilated ovarian venous system is found to run in a common fascial sheath with the ureter and this close apposition may result in secondary ureteric changes.

Surgical treatment by ligation of the ovarian vein(s) cures the condition and should be offered as treatment of intractable symptoms A small extraperitoneal oblique abdominal incision is adequate for the procedure which entails simple ligation of the vein(s).

Reference

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The Inferior Polar Vessel in Hydronephrosis

By H. W. GOWLAND, FRCS

The Wellington Hospital, Wellington, New Zealand

An artery to the inferior pole of the kidney may arise from the main stem renal artery or directly from the aorta. Such vessels usually run anterior to the upper ureter or pelvi-ureteric junction before entering the kidney through the hilum or the convex border; vessels passing behind the ureter have been recorded. Prior to the development and wide practice of pyeloplasty, congenital hydronephrosis with lower polar vessels sometimes received ineffectual treatment by leaving the vessels *in situ* so that not infrequently nephrectomy was subsequently required. Attempts to transpose inferior polar vessels up to the level of the main pedicle sometimes proved difficult and were not always rewarding. Division of small vessels may not have done great harm but did not always do clinical good.

Pyeloplasty has proved satisfactory, particularly in respect of relief of symptoms and not necessarily with marked pyelographic improvement. The use of the Anderson Hynes procedure conveniently allows the transposition of the pelvi-ureteric junction to lie anterior to any inferior lower polar vessels.

Hydronephrosis occurs commonly in the absence of polar vessels which in the event are not infrequently present without associated hydronephrosis. Personal experience inclines one to the view that inferior polar vessels exert a purely secondary influence in hydronephrosis.

Retroperitoneal Fibrosis

By H. G. WATTS, FRCSE, FRCS, FRACS

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Since the first description of retroperitoneal fibrosis in 1948 some hundreds of cases have been reported but series from individual centres are small. During the past 3 years, 5 cases of retroperitoneal fibrosis, causing ureteric obstruction, have been diagnosed in Tauranga, and of these 3 were classified as idiopathic, 1 was associated with prolonged Deseryl (methysergide) medication and the fifth patient presented with ureteric obstruction following irradiation therapy and surgical treatment for carcinoma of the cervix but with identical histological findings to the other 4 patients.

Each of the 5 patients presented with typical radiological changes of hydronephrosis and upper ureteric dilatation. Whenever it was attempted, ureteric catheterisation was easy and was not followed by urinary infection. A preoperative diagnosis by perfusion pyelography sometimes supported by retrograde pyelography was made in all 5 cases and they were subjected to ureterolysis and multiple deep biopsies of the retroperitoneal tissues. Improvement of renal function and regression of the upper urinary tract dilatation occurred in all patients following surgical treatment.

These cases did not provide new concepts of aetiology which remains obscure. Some cases are due to retroperitoneal infection, urinary leakage or haemorrhage, whilst others are causally related to medication with methysergide or other anti-serotonin agents but in most cases no cause can be defined. Males are more frequently affected but in this series 4 of the 5 patients were women.

Symptoms are non-specific; malaise, back ache, frequency of micturition, oliguria, weight loss and nausea are common. There may be oedema of the legs or scrotum. The erythrocyte sedimentation rate may be raised, protein electrophoresis is often abnormal and uraemic states are common. No generalised collagen disease or arteritis has yet been identified but mediastinal fibrosis, Riedel's thyroiditis or sclerosing cholangitis may co-exist.

At operation, retroperitoneal fibrosis is predominantly peri-aortic in distribution and spreads laterally to surround and entrap the ureters. Histologically there is dense fibrosis with infiltration with chronic inflammatory cells and thickening and obliteration of the smaller blood vessels. The main differential diagnosis is from retroperitoneal tumours, both primary or secondary and multiple biopsies are needed for exclusion.

Treatment consists of withdrawal of any methysergide medication, administration of steroids and in most cases ureterolysis. Both ureters may be freed through a transperitoneal approach after medial reflection of the colon. Splintage and nephrostomy drainage are not required when the ureter is not damaged. Follow-up surveillance is essential because ureteric entrapment may recur.

Primary Carcinoma of the Ureter

By B. G. STOREY, FRCS, FRACS,
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Primary carcinoma of the ureter is rare and only accounts for an estimated 1% of all carcinomas of the upper urinary tract; it is found in one out of every 11,000 autopsies, but during the past three decades it has been diagnosed clinically at an increasing rate.

This series of 6 patients included only 1 female and the ages ranged from 48 to 73 years. Painless haematuria was the presenting symptom in 4 patients and pain in the remaining 2. All tumours were solitary and 4 tumours occurred in the distal third of the left ureter.

Intravenous pyelography was performed in 3 patients and showed hydronephrosis in 2 and loss of renal function in 1 patient. The correct diagnosis was not suspected in any of these patients but retrograde pyelography revealed gross abnormality of the affected ureter in all the patients.

Cystoscopic findings were normal in 5 patients, bloody efflux was seen coming from the ureteric orifice in 1 patient whilst in another a recurrent tumour was seen to protrude from the ureteric orifice some 3 months after complete removal of the ureter at nephro-ureterectomy.

The ureteric tumour was managed in 4 patients by one stage nephro-ureterectomy with excision of a bladder cuff; this excision was incomplete in 1 patient and was followed by local recurrence within 3 months. A fifth patient underwent a two-stage nephro-ureterectomy whilst the sixth patient underwent excision of the ureteric stump in which a squamous cell carcinoma had developed some 10 years after nephrectomy for chronic pyelonephritis. Primary tumours arising in the ureteric stump are very rare and only 15 cases have been reported previously; half of these were squamous cell carcinoma which proved fatal within 3 years. The patient in this series with squamous carcinoma died 6 months after operation from generalised metastases.

It is interesting that the only female in this series also suffered from analgesic nephropathy and it could be conjectured that future study may reveal a higher incidence of primary carcinoma of the ureter similar to the increased incidence of tumour of the renal pelvis in association with analgesic nephropathy.

Urinary Calculus

By J. P. BLANDY, MA, DM, MCH, FRCS

The London Hospital, London

Since the turn of the century, the pattern of urinary calculus has changed and instead of stone in the bladder—the basis and origin of all surgery—we are now faced with a steadily increasing incidence of upper tract calculi. Many of these upper tract stones are very small, pass easily after a few episodes of colic, and pose little or no problem for the surgeon. Unfortunately most of the studies on the aetiology of stone formation have concerned themselves with these small and (for the surgeon) unimportant calculi, and have attempted to express the cause of stone in simple biochemical terms. But the real problem for the surgeon is in connection with the less common, but far more dangerous, large laminated calculus, so often associated with urinary infection and obstructive uropathy. Among 429 selected patients studied in The London Hospital Stone Clinic, 311 operations were required, only 73 of which were for ureteric calculi, while 190 were performed for stones in the kidney, mainly in women (122) rather than in men (68). It is suggested that the proper target for our attention should be these large "surgical stones"; and some of the methods we have been using include the electron microscopy of these calculi and their non-calcified matrix, the attempt to "band" the stone-laminae with various substances, and studies of the diffusion through calculi of antibiotics. As for treatment, we have studied 85 operations for large branched calculi in 73 patients aged from 6 to 76 years. Infection was present in 71% before operation. There was no operative mortality. Six wound infections occurred. No secondary haemorrhage or nephrectomy was required.

In 17 kidneys, calculi or fragments were left behind but passed spontaneously in 4, remained unchanged in 9 and formed the basis for new calculus formation ("false recurrence") in 4 patients. It is evident that small residual particles of calculus are only one among many factors which may be responsible for the recurrence of large urinary calculi and it is further evident that much remains unknown.

Metabolic Aspects of Urinary Calculi in Wellington

By R. B. I. MORRISON, MD, CHB, MRACP

Wellington Hospital, Wellington, New Zealand

In the 4 years between January 1969 and December 1972, 322 patients with renal calculi have been studied. There were 249 (77%) men and 73 (23%) women. Women (mean age 35 years) passed their first stone at a younger age than men (mean age 40 years).

All patients were interrogated by a physician, paying particular attention to factors which are known to influence stone formation, and by a dietitian who assessed their intake of calcium and oxalate.

Two 24-hour urine, and 2 fasting blood samples were collected, and phosphate clearance and urinary acidification were measured during attendance at the metabolic ward for half a day. Midstream urine samples were checked for infection and amino acids, and all stones were qualitatively analysed.

Almost half of the patients (156) had passed an earlier stone; significant numbers had a positive family history of calculus disease (41), a history of prolonged immobilisation (47), urinary infection (47), dyspepsia (91), a period in the tropics (37) or a heavy analgesic intake (17).

The mean serum calcium level was 10·2 mg %. Seven patients had levels greater than 11·0 mg %, 3 of whom had a parathyroid tumour, 3 now have normal values and 1 has left Wellington. One patient had a value less than 9·0 mg % but no cause has been found for this low level.

81 patients excreted more than 300 mg of calcium per day (average of two values). In this group, 33 (41%) had a dietary intake of more than 1000 mg of calcium per day compared with only 21 (9%) of the remaining patients. It is important to assess the salt balance when interpreting urine calcium excretion.

Qualitative analysis of 146 stones showed that 104 contained calcium, phosphate and oxalate. Quantitative analysis is recommended.

The following diagnoses were made: idiopathic hypercalciuria 73, hyperparathyroidism 5, uric acid stones 12, renal tubular acidosis 7, cystinuria 2.

A positive history of some event known to influence stone formation was elicited in 99 patients; 54 had an estimated dietary calcium intake greater than 1,000 mg, while in 70 patients no possible cause was found. A stone may be passed years after its formation, when exhaustive tests will reveal no abnormality.

All stone formers should pass through a planned investigation so that possible causes may be identified, and the effects of treatment and the natural history observed.

Surgery of Cast Calculi with Kidney Cooling

By W. Gregoir

Hospital Brugmann, Brussels

We have been using, for several years, 2 methods for kidney cooling in the difficult surgery of cast calculi or complicated lithiasis. One method consists in cooling the kidney with a rubber mattress where a cold alcoholic solution circulates; it is particularly useful when the cooling time has to be long. For shorter operation however, we prefer the method of Boyce whereby the kidney is cooled very quickly with slush ice. Kidney cooling has proved to be very efficient for the removal of staghorn and multiple calculi; it allows the operation to proceed in a dry field under clear vision; it prevents any exaggerated loss of blood, allows for pyeloscopy and pre-operative X-ray controls. The temperature of the kidney should be low, under 15° centigrade; the renal artery may be clamped during 90 minutes. Occasionally but not always, cooling is followed by a short period of renal insufficiency very comparable to the phenomenon commonly observed after kidney transplantation. We have never observed a single case of definitive impairment of the renal function after cooling. The method has been used very successfully for the removal of a centrorenal malignant tumour in a single kidney.

Urinary Calculi in Children

By P. J. M. Retief, chm

Red Cross War Memorial Hospital for Children, Cape Town, South Africa

Between 1958 and 1972, 53 children under the age of 13 years were seen with urinary calculi at the Red Cross Hospital in Cape Town. The average outpatient attendance at this hospital is about 175,000 children per annum with an average ward admission rate of about 5,000 per annum. The total number of cases seen in relation to the total number of patients which pass through the hospital is not great, but at least 3 or 4 children with urinary calculus are seen each year.

An investigation into the incidence and variety of calculi occurring in childhood in the Cape Province became practical after 1956 when large numbers of children were channelled into the one institution. It is also important to the analysis to note that this hospital cares for the 3 main racial groups in the area, namely white, Cape Coloured and Bantu. The Bantu are a Negro race, the Cape Coloured a mixed race and the whites are Caucasian. The Bantu and Coloured people are the poorer section of the community.

It is significant that of the 53 children with calculi 48 were Cape Coloured, 5 were white and none were Bantu. It is also noteworthy that there were 46 boys and 7 girls and that 38 children had bladder and urethral calculi and only 15 had stones in the kidney or ureter. There were only 2 girls who had bladder stones and no bladder stone was found in a white child. It is clear, therefore, that bladder and urethral stones occur far more often in the Cape Coloured community, which is the poorer section and it is possible that a socially similar group, namely the Bantu children, have a protective mechanism against calculi.

It is well known that until 50 years ago bladder calculus in boys was a common surgical disorder in most countries. This disease has virtually disappeared in European and American societies and now the incidence is limited to certain localities in the Near and Far East. It has also been shown that bladder calculi are endemic in areas where nutrition is largely dependent on a single cereal food and deficient in protein and dairy products. These endemic calculi are limited largely to young boys of the poorer section of the community. The chemical composition is most often uric acid or urates. These calculi frequently form in sterile urine and in a urinary tract which is otherwise normal.

From this study of urinary calculi in the Cape Province it is clear that this is an endemic area for stones, but only to a limited degree. No specific dietary deficiency has been established and there may be other factors like dehydration due to gastro-enteritis.

It is a matter of interest that in this series of cases there was a reasonably high incidence of associated post-obstructive renal atrophy and pyelonephritis which suggests that the calculi form in the kidney and grow secondarily in the bladder. The rarity of bladder calculi in girls is due to an anatomical reason.

Although it is suspected that urinary grit frequently passes down the ureters in children causing ill-defined abdominal pain, ureteral colic, with radiological proof of an impacted ureteral calculus, is very seldom encountered.

Prostatic Carcinoma

By J. D. FERGUSSON, MD, FRCS

The Institute of Urology, University of London

Current research at the Institute includes the following items:

(i) Scintigraphy—using polyphosphate labelled with technetium—99 m in the early diagnosis of bone metastases.

(ii) Radioimmunoassays of the plasma testosterone during treatment with synthetic and natural oestrogens (in various dosages) and also after orchidectomy and pituitary ablation.

(iii) Immunological studies relating to host resistance (as shown by the lymphocyte transformation rate) and the spread of the disease.

(I) *Scintigraphy*. During recent years various radioactive preparations have been used in conjunction with the Gamma camera for skeletal scintigraphy. Some of these have exhibited practical drawbacks (fluorine-short half-life, strontium-inadequate definition and indefinite skeletal localisation). Moreover, the positive yield in terms of metastatic deposits previously unrevealed by conventional radiography has been relatively small.

The use of technetium-labelled polyphosphate (Diagnostic Isotopes Incorporated) would appear to have definite advantages in that not only are early metastases clearly shown in relation to the surrounding bone topography but the duration of the examination is reduced from 1 hour (strontium) to 15 minutes and the cost is considerably less. Simultaneous scintigrams of the kidneys and bladder may also aid in localisation.

(ii) *Plasma testosterone assays*. Until recently assays of the serum testosterone using biological standards were time consuming, often unreliable and expensive. The advent of a new method of radioimmunoassay (as practised by Professor Somerville at the Chelsea Hospital for Women, London) has provided a means of determining the response to different methods of endocrine-control therapy. Our preliminary investigations have shown a striking fall in the plasma testosterone content in response to orchidectomy and pituitary ablation. It is of wider practical importance that a similar reduction has been observed in cases treated with stilboestrol in doses varying between 50 mg and 5 mg a day, with Premarin 1·5 mg daily but *not* with TACE. It remains, of course, enigmatical whether the fall in serum testosterone accurately reflects the response to treatment.

(iii) *Immunological studies*. In line with investigations on the spread of cancer of the breast, similar studies have been made using the lymphocyte transformation rate as an index of host resistance. In this test the patient's lymphocytes are separated, radiolabelled and incubated with phytohaemagglutinin, which stimulates them to proliferate. An appropriate sample is then submitted to a scintillation count. Some measure of correlation has been observed between the rate of proliferation (host resistance) and the degree of spread (activity) of the disease.

Experience with the Gregoir-type Prostatectomy

By D. LENAGHAN, MS, FRCS, FRACS

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This is a retropubic prostatectomy which aims to minimise bleeding by certain preventive haemostatic techniques. A pedicle comprising anterior vesicocapsular branches of the inferior vesical arteries and veins is ligated in front of the bladder and lateral to the prostate on each side. Sutures are placed at the prostatic apex, in the vesico-prostatic capsule and vesical adventitia below and above the transverse capsular incision. After the usual enucleation and resection of the bladder neck, posterior haemostasis is achieved by a series of trigonisation sutures. The main sutures are those placed postero-laterally in the prostatic capsule, one on each side; each is introduced from outside the capsule, passes through the bladder neck and out through the capsule, pulling the trigone downwards and laterally and controlling most of the bleeding. Additional small sutures between the two lateral ones further fix the trigone into the upper part of the prostatic cavity. Continuous irrigation is used postoperatively.

In a series of 59 patients there was no mortality; three-quarters of the patients required either no blood transfusion or a single unit only. Most patients had their catheters removed by the third postoperative day and about half the patients were discharged from hospital within 10 days.

Carcinoma of the Urachus

By H. M. LEAROYD, FRCS, FRCS(ED), FRACS

Sydney Hospital, Sydney, N.S.W.

Carcinoma of the urachus is a rare tumour of which treatment is almost invariably unsatisfactory and the prognosis poor.

The pathogenesis of urachal tumours is not known but they have been variously regarded as metaplastic transformations of epithelium, proliferations of normal adenomatous structures in the intramucous part of the urachus or embryonic inclusions of intestinal epithelium. The most common malignant tumour of the urachus is adenocarcinoma which may be mucus secreting and may be combined with transitional epithelial carcinoma and/or squamous carcinoma.

The clinical presentation of urachal carcinoma does not differ significantly from that of other bladder tumours; 1 of the 2 patients reported presented with the passage of mucus in the urine whilst the other complained of haematuria. It is important to differentiate between adenocarcinoma developing in transitional epithelial cancer and carcinoma of the urachus as a primary lesion. The primary bladder cancer develops in the mucus membrane and invades the muscular layer as it progresses whilst carcinoma of the urachus develops primarily in or outside the bladder wall and any invasion of the mucus membrane occurs at a later stage.

The classical method of treatment has been by extended partial cystectomy but recently it has been emphasised as important to remove not only the bladder vault but also the overlying peritoneum and connective tissue in the cave of Retzius. In most of the recorded cases partial cystectomy was carried out but with a disturbing incidence of recurrence of tumour in either the abdominal wall or pelvis in no less than 30% of patients so treated. This high incidence of local recurrence of adenocarcinoma which does not usually show any tendency to wound implantation strongly suggests incomplete excision of the primary tumour in many instances. Transurethral resection of the tumour is usually inapplicable and irradiation therapy is usually ineffective.

The prognosis in this disease is poor with less than 10% 5-year survival rate. This extremely unfavourable prognosis may be related to the development of the tumour over a prolonged period without symptoms and the tendency towards infiltration into the abdominal wall.

Carcinoma of the Kidney—Diagnosis and Angiographic Evaluation

By W. Gregoir

Hospital Brugmann, Brussels

Selective arteriography confirms the diagnosis of a renal carcinoma and gives a fair idea of its geographic extension; however, cavography is indispensable for the diagnosis of renal vein invasion. The method is simple and devoid of danger. Contrast medium is injected into both femoral veins. Opacification of the vena cava should be very strong; most of the mistakes in the diagnosis are secondary to insufficient opacification. Invasion of the renal vein and the vena cava is marked by an irregular and lacunar image and may be accompanied by signs of caval stasis. It should not be confounded with false lacunar images like the impression of the hypertrophic renal artery on the posterior wall of the vena cava, the very special image of the renal venous flow and images of compression without invasion. Evidence of caval invasion is not necessarily a contra-indication to a radical nephrectomy; it is of course of very bad prognosis but thrombectomy or even partial resection of the lateral wall of the vena cava may give an appreciable and comfortable though limited survival. However, the radiological evidence of caval invasion in a tumour secondary to Thorotrast impregnation must be considered as an absolute contra-indication to a nephrectomy since it always means a direct invasion of the caval wall by the tumour directly from outside and not the presence of a simple neoplastic thrombus coming out of the renal vein.

Carcinoma of the Kidney

By J. P. Blandy, MA, DM, MCH, FRCS

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Rescrutiny of the results of adding postoperative radiotherapy to nephrectomy raises the possibility that in some cases the host's defence against the activation of small scattered metastases may be impaired, and no matter what local destruction of the tumour is accomplished, the effect upon the immune defences may be harmful and impair survival. Similar consequences may follow preoperative radiotherapy and only blind prospective controlled studies will determine the truth. However, difficulties arise in carrying out such a prospective study, many of which concern the accuracy of diagnosis before nephrectomy. Increasing experience with ultrasonic scanning and arteriography offers a significant improvement in diagnostic accuracy and the use of needle puncture of the suspicious mass seems justified in selected cases. The unpredictable behaviour of carcinoma of the kidney, especially those advanced cases who survive without treatment, forces us to reconsider the role of surgical excision of bulk tumour tissue as well as the possible hazards of radiotherapy.

The Use of Ultrasound in the Diagnosis of Extension of Malignant Renal Tumours into the Inferior Vena Cava

By R. D. Wines, FRCS(ED), FRCS, FRACS,
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The inferior vena cava is involved in malignant renal tumours in 5 to 10% of cases by direct spread or by extension along the renal vein. Knowledge of caval extension may necessitate modification of surgical approach to allow for attempt at total tumour removal or prevent dissemination and massive pulmonary embolisation.

The inferior vena cavagram is the usual method of preoperative diagnosis but interpretation is often difficult because of the "streaming" effect of renal venous flow.

In this study attempts have been made to detect vena caval extension with the directional Doppler by the following method.

A probe is located over the femoral vein to produce an ultrasound beam which is directed obliquely through the blood stream. The probe also records the reflected ultrasound which changes in frequency in proportion to blood flow. Normal flow is intermittent with decrease on inspiration whilst Valsalva manoeuvre produces a decrease or reversal of flow. In total caval occlusion flow is continuous and is not effected by respiration or Valsalva; in partial occlusion of the cava the flow patterns are attenuated and the effect of Valsalva is barely demonstrable.

Doppler studies were carried out on 9 patients with renal space-occupying lesions. In 4 patients with angiographic evidence of benign renal lesions (3 cysts, 1 calcified subcapsular haematoma) the Doppler findings were normal. In the group of 5 patients with malignant renal masses, 3 patients had normal Doppler findings whilst 1 showed partial and 1 total occlusion of the vena cava.

Ultrasound studies thus produced results which correlated with vena cavagrams and operative or post-mortem findings in 4 of the 5 cases with malignant renal disease. In the fifth patient the false negative finding was associated with involvement of the right side of the inferior vena cava by direct extension of the renal tumour rather than by intraluminal spread.

These preliminary studies suggest that useful information may be obtained by this simple Doppler procedure but similar difficulty as occurs with cavography will be encountered in the detection of small intraluminal extension of tumour which is not associated with significant alterations in caval blood flow.

Painless Nephrectomy

By P. HARBISON, FRCS, FRACS

Queen Elizabeth Hospital, Adelaide, S.A.

Posterior approaches to the kidney have distinct advantages in some types of renal surgery. Division of muscles is avoided in contrast to loin incisions and postoperative pain and morbidity are less.

Lumbotomy as advocated by Professor Gil Vernet of Barcelona exposes the kidney through the lumbar fascial aponeurosis. Renal surgery is carried out easily provided adequate retraction is available and the surgeon is familiar with the technique. Indications for lumbotomy are:

1. Nephrectomy for pyelonephritis, hydronephrosis or calculi.
2. Pyelolithotomy.
3. Upper ureterolithotomy.
4. Nephro-ureterectomy.

The approach is not recommended for difficult renal surgery because exposure may be limited.

Nephro-ureterectomy can be performed in an almost painless manner by lumbotomy combined with vaginal excision of the ureter after passage of a splint to facilitate localisation of the lower ureter. This procedure is suitable for the management of pyelonephritis kidneys with reflux.

Bilateral nephrectomy through the beds of the 12th ribs or with sub-costal incisions is indicated for:

1. Pre-transplant nephrectomy.
2. Malignant hypertension.

Adrenalectomy can also be performed through these incisions. Morbidity from the posterior approach is far less than that which follows the anterior or bilateral loin approaches; this is a very important consideration in the management of very sick patients. The technique is safe and rapidly performed but satisfactory positioning of the patient on the operating table is an important feature.

Liposarcoma of the Kidney

By A. BOGDAN, MD

Fairfield District Hospital, Sydney, N.S.W.

Liposarcoma of the kidney is a rare tumour and only 29 cases were reported in the literature prior to 1960; very few additional reports have appeared since then and none has derived from Australasia.

The lipoblasts of the tumour could arise from totipotent cells within the capsule of the kidney or could invade from the perirenal fat. Half of the reported cases were in conjunction with the curious syndrome of tuberous sclerosis with adenoma sebaceum and mental retardation. The tumour is radioresistant but a large percentage of the reported patients survived nephrectomy for longer than 5 years.

In this reported case renal pain and haematuria appeared one year after resection of Grade I papillary bladder tumour. The liposarcoma was attached to the renal pelvis and was invading the lower pole of the kidney. Metastases appeared 3 months after nephrectomy and the patient died 7 months after the operation. In this patient there were no signs of the syndrome with tuberous sclerosis.

Renal Tuberculosis in New Zealand

By A. F. FERGUSON, MB, CHB, FRCS, FRACS

The Wellington Hospital, Wellington, New Zealand

The general incidence of tuberculosis in New Zealand is steadily decreasing despite an increase of population, due to improved living conditions, efficient chemotherapy and preventive measures.

B.C.G. vaccination which has been for some years given to both adolescents and contacts has recently been extended to vaccination of babies in groups at risk, that is particularly Maoris and Pacific Islanders.

The total figures for new cases of genito-urinary tuberculosis have not shown a similar decline, but this should be expected because most of the cases have a history which extends over 10 to 20 years so that the primary infection often occurred prior to the introduction of effective chemotherapy.

59 cases of genito-urinary tuberculosis were treated in Wellington Hospital between 1960 and 1969. The majority of patients presented with persistent urinary infection, and delay in diagnosis appears to be the rule. 60% of all cases were well advanced at the time of diagnosis. Of the group of 59 cases, 39% were Polynesian, 55% Europeans of New Zealand origin, and 21% occurred in European immigrants who had their primary disease before coming to New Zealand. The incidence amongst immigrants was much lower than that reported by Jose in the Proceedings of the Twenty Third Annual General Meeting of the Society in 1970 although the immigration rates into New Zealand and Australia have been similar.

Treatment has been by standard triple drug regime, used for 3 months or until the urine has become sterile. Where drug sensitivity occurred, another antituberculosis drug has been substituted. In the past 2 to 3 years there has been a tendency to replace PAS with Rifampicin, which is similar in its effectiveness but very much simpler for the patient to take.

Despite a conservative or generally non-surgical approach to the disease, surgery has been needed in a significant proportion of cases. In a group of 23 cases with radiological evidence of only minimal renal lesions, 3 patients required surgical treatment of associated testicular lesions. There were 16 cases with moderate unilateral lesions and in this group there were 5 nephrectomies; each of these nephrectomies was carried out in the first 2 years of the review and before the triple drug regime had been standardised. Of 15 patients with severe unilateral lesions 11 nephrectomies, 1 reimplantation of the ureter and 1 partial nephrectomy were performed. Unilateral nephrectomy was required in 3 out of 5 patients with severe bilateral renal involvement.

In two-thirds of the patients undergoing nephrectomy the operation was indicated by non-function of the kidney and in the remainder nephrectomy was required to relieve continued complications and symptoms in very severely affected kidneys. Stricture formation has not been a great problem, although ureteric reimplantation was required in 1 patient.

Genito-urinary tuberculosis in New Zealand appears to be decreasing at a slower rate than pulmonary tuberculosis, but the incidence may well show a more dramatic fall in the next few years.

Infertility

By J. P. BLANDY, MA, DM, MCH, FRCS
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Simple clinical examination of the infertile male will detect gross endocrine abnormalities such as Klinefelter's syndrome, or the scars of previous explorations of the groin, or an uncorrected varicocele. A grossly impaired semen volume suggests vesicular disease. Absence of spermatozoa from the ejaculate may be due to mechanical blockage which can be displayed by radiography after injection of contrast medium into the vasa and corrected by vasovasal or epididymovasal anastomosis in some cases. In oligozoospermia, or when no block can be found, then testicular biopsy may avoid fruitless attempts at therapy by showing germinal cell aplasia and offer some hope of improvement by showing the "sloughing effect"; in such cases significant improvement in sperm density occurred in one third of two groups of patients empirically given fluoxymesterone or clomiphene although at present we have no means of predicting which men will respond and which will not. Spermagglutinating antibodies were present in 2% of fertile men and 14·7% of 144 infertile men and may have been related to the cause of their infertility, but again no simple pattern emerges from a limited series studied by vasography and testicular biopsy.

The Co-ordination of Care for Myelomeningocoele Patients

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With the decline of skeletal tuberculosis, chronic osteomyelitis and poliomyelitis, meningomyelocoele and cerebral palsy have become the two most important serious crippling diseases of childhood. Assuming an incidence of spina bifida cystica of 1 to 2 per 1000 live births, then it is estimated that between 60 and 120 babies with this condition are born annually in New Zealand. With a modern therapeutic approach some 55% of these patients survive to school age and less than 10% of those are totally ineducable.

A large number of surgical specialists are involved in the care of the spinal lesion, the accompanying hydrocephalus which develops in 80% of cases, and the orthopaedic and the renal problems concomitant with any associated paraplegia.

Total care of the child as an individual, the problems of the family and the educational problems demand a team approach with medical personnel supported by ancillary paramedical services and educational facilities. A paediatrician is perhaps best suited to oversee the total problem. Valuable help may be obtained from an experienced trained nurse who visits the children in their homes and maintains contact with the hospital specialists and the family doctor.

Colocystoplasty—Bladder Replacement after Total Cystectomy for Carcinoma

By P. T. BRUCE, CHM, FRCS, FRACS

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The formation of an artificial bladder following removal of a diseased bladder has exercised the minds of surgeons for nearly a century. A segment of ileum, the caecum and a segment of pelvic colon have all been used with varying successes. Any good alternative to the present-day methods of urinary diversion (ileal conduit or ureterosigmoidostomy) is, therefore, welcome.

Professor G. B. Ong of the University of Hong Kong, between 1963 and 1969 performed 21 colocystoplasties, fashioning a new bladder from an isolated loop of sigmoid colon. The colon was not used as a long loop but was incised along the antimesenteric border and sewn up in such a manner as to produce a vesicle which was then anastomosed to the urethra just above the external urethral sphincter; the ureters were anastomosed to the new bladder.

This technique has been used in 10 colocystoplasties since 1968 in the management of patients with carcinoma of the bladder. The series included 1 female and 9 male patients with ages ranging from 45 to 72 years. There was no operative mortality but there was formidable postoperative morbidity. The female patient who had a carcinoma of the bladder involving the vagina died 8 weeks after operation from metastatic disease; 1 male patient died 21 months after operation also from metastases but he had remained well in the postoperative interval despite some nocturnal incontinence controlled by a penile clamp.

5 of the 8 patients who are still alive are leading a near normal life but 4 of them require to wear a penile clamp at night whilst 1 patient is perfectly continent by day and night.

4 of the 10 patients have a chronic lower urinary tract infection which requires long-term antibiotic therapy in management; the other patients have passed sterile urine. Though each of the patients passes mucus with urine only 3 patients have excessive mucus loss with potassium depletion which requires oral supplement. One patient has chronic uraemia and has survived operation for almost 2 years despite a pre- and postoperative level of blood urea at 100 mgs%; he wears a penile clamp to control incontinence by day and night. One patient developed a fistula between the colonic bladder and the rectum but the fistula eventually sealed after the third operative closure by the York-Mason technique.

During this series some variations in technique have been introduced. A longitudinal abdominal incision is now preferred because of high incidence of incisional hernia formation at the transverse incision used in the first 5 patients. The anastomosis of the colonic bladder to the urethra is done with interrupted Dexon sutures rather than continuous chromic catgut suture which was followed by stricture formation in 2 patients; the strictures have stabilised after instrumental dilatation.

Experience with this series of 10 patients over 5 years gives the impression that the operation is worthwhile despite some formidable postoperative complications. It is considered that colocystoplasty is probably the most physiological method of replacement of the bladder currently available and should be considered as a reasonable alternative to urinary diversion after cystectomy.

Two Primitive Urethral Operations in Oceania: Subincision in Australia and Thoka-losi in Fiji and the Tonga Islands

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Two primitive urethral operations have been practised in Oceania, subincision in Australia and thoka-losi in Fiji and the Tonga Islands. The former is a rite of initiation and the latter a form of surgical treatment but there is no convincing explanation of the extraordinary use of urethrotomy in these procedures. The occurrence of these practices in the same small segment of the globe and the close similarities of variants of the two procedures suggest a common origin in some forgotten ancestral rite.

Urethroplasty

By J. P. Blandy, MA, DM, MCH, FRCS

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Although careful, regular and gentle, bouginage remains the main method of treatment of the majority of urethral strictures, in the last decade the use of full thickness pedicled skin as a urethral inlay has offered the chance of a radical cure and a permanent relief to the sufferings of many of these men. In the last 9 years, 141 urethroplasties were performed of which 29 were for "easy" strictures confined to the anterior urethra, and the remaining 112 were for full-length or difficult, high, and often complicated posterior strictures. Increasing familiarity with the inverted U-shaped scrotal flap has made it possible to adopt it as a one-stage procedure (7 cases) for relatively short posterior strictures or, by forming the flap into a long tube over a silastic splint, to make use of the flap as a pull-through substitute for the urethra where gross dislocation or scarring has followed a rupture of the posterior urethra (5 cases).

Re-stenosis in the 2-stage operations occurred in 4 instances, all of which were successfully revised and the operation subsequently completed. Failure, *i.e.* stricture recurrence after completion of the second stage or after one stage operations, occurred in 6 out of 141 cases (4·3%) but 2 of these men had had further attacks of gonorrhoea and one is a depressed psychotic man who insists on bouginage though a urethrogram fails to show any new stricture. It is likely, however, that as the series continues there will be a few more late re-stenoses as time goes by.

Continence is curiously unaffected by urethroplasty even when the skin flap has to be taken right up into the bladder and all the known sphincters have had to be divided. Three wet men remained wet after urethroplasty (for post-T.U.R. strictures performed elsewhere); 3 who were wet because of constant leakage from fistula became dry; 2 who had been continent after prostatectomy became wet after urethroplasty—and one of these is very doubtful. Impotence has not been a complication of any of these operations.

The Anatomy of the Urethral Stricture

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A post-mortem study of the anatomy of urethral stricture was carried out at the Mulago Hospital, Kampala, in Uganda. The findings in 22 specimens of urethra, prostate and bladder demonstrated the whole process of development of stricture from the initial post-gonococcal scars through squamous metaplasia of the urethral epithelium to the formation of a complete ring of collagen. There was no evidence of bacterial infection in these specimens.

Examination of the established stricture revealed that sterile inflammation occurred extensively in areas of high mural pressure and that new collagen was formed continually at the proximal face of the stricture.

It is postulated that squamous metaplasia occurs at some time after gonococcal infection and that this inelastic, unsupported epithelium ruptures repeatedly under the distending pressure of the urinary stream. Scar tissue accumulates in the sub-epithelial connective tissue until at one point a complete ring is formed. The urinary stream now impinges directly upon the whole proximal face of the collar and a continuous inflammatory process results. New collagen is formed and the collar extends proximally and gradually tightens with contracture. As the lumen narrows the voiding pressure rises and the inflammatory process accelerates.

Urethritis and the Urethral Syndrome in Stress Incontinence

By G. F. Murnaghan, MD, CHM, FRCS

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In a series of 71 female patients with an age scatter between 30 and 65 years of age, presenting with stress incontinence of urine, an associated history of frequency, scalding and urgency with micturition (to comprise the urethral syndrome) was obtained in 29 patients (41%).

An endoscopic diagnosis of proximal urethritis was made in 69% of those patients with simple stress incontinence as compared with 76% of those patients with multiple symptoms.

Lateral exposure still cystography was applied to each of these patients at rest, during straining and during attempted voiding and the effect of these manoeuvres upon the posterior urethro-vesical angle was measured.

Loss of the posterior angle during straining was found in 62% of those patients who had pure stress incontinence but in only 35% of those patients with stress incontinence complicating the urethral syndrome.

58 patients of the entire group were available for follow-up surveillance for significant periods of time ranging from several months to 5 years; the 2 subgroups of simple stress incontinence and incontinence combined with urethral syndrome contained 35 and 23 patients respectively. In these follow-up groups the incidence of loss of angle at the time of first assessment was 60% of the 35 patients and 39% of the 23 patients. In those patients of these symptomatic groups who were thought to have sufficient proximal urethritis to merit diathermy treatment the incidence of loss of angle was 50% in each of them.

No marked or useful correlation emerged between loss or preservation of the posterior urethro-vesical angle during straining in association with stress incontinence, with or without proximal urethritis as judged either by history of the urethral syndrome or by endoscopic diagnosis at the time of first assessment.

In the follow-up analysis it was noted that amongst those patients whose stress incontinence had proved so troublesome and persistent as to require pelvic floor repair or some other form of surgical treatment, the incidence of loss of angle at first assessment was 78%. This incidence was twice that found in those patients in whom there was either significant improvement in urinary control to justify postponement of any operative treatment or who experienced complete alleviation of symptoms following diathermy treatment of proximal urethritis and treatment of any concomitant urinary tract infection or genital sepsis.

There was a striking contrast in the incidence of loss of angle at 78% in those patients with pure stress incontinence who required pelvic floor repair as compared with an incidence of 18% in a smaller group of patients who had the urethral syndrome with stress incontinence but who had significant improvement without pelvic floor repair after treatment of proximal urethritis.

In female patients with stress incontinence of urine, conservation of the posterior urethro-vesical angle on straining cystography is a useful prognostic sign to be used as an encouragement in the direct attack upon any proximal urethritis with hopeful anticipation that such conservative treatment will give significant relief to 50% of the patients.

These studies were supported by a Grant-in-aid from the Australian Kidney Foundation.

An Evaluation of Urethral Pressure Profiles

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A method of recording urethral pressure profiles has been devised using a motorised constant flow apparatus and continuous transmission of pressure changes for recording and display on a storage oscilloscope during withdrawal of the urethral catheter. Polaroid photographs of the recordings were obtained.

Experiments were conducted on 22 female greyhounds and were designed to assess the effect of various factors including dissection, mobilisation, drugs and pudendal nerve stimulation upon the urethral pressure profile.

In the intact healthy urethra there is a slight increase in profile as the catheter is withdrawn to encounter the bladder neck and the profile shows a gradual increase to a maximal peak in the mid or distal portions of the urethra where striated muscle predominates; there is a rapid fall to zero as the catheter reaches the external urethral meatus. A marked increase in the height of the mid-urethral peak without any change in the bladder neck and proximal urethral portions of the profile followed exposure and stimulation of the pudendal nerves in the ischio-rectal fossa. Contraction of the distal striated musculature was followed by elongation and stretching of the proximal portion of the urethra so that the actual area of urethral resistance increased and the urethra increased in total length. However, the distal urethra did in fact shorten despite this increase in total urethral length so that the apex of the mid-urethral peak of the profile moved towards the external urethral meatus.

When the urethra was dissected from the surrounding striated muscle component there was complete loss of distal urethral resistance as compared with the pre-dissection baseline profile to suggest that striated muscle provides a fair degree of tonus to the urethra in the basal state. After dissection stimulation of the pudendal nerves did not increase the distal urethral resistance.

When the urethra was completely detached to lie free from the distal and vaginal attachments to form a continuous tube with attachment at the bladder neck, then the proximal urethral profile still retained its basic normal form with persistence of bladder neck indicating the continual effect of smooth muscle in the maintenance of proximal urethral resistance. If the mobilised urethra was manually lengthened to allow the bladder neck to move distally then there was an increase in urethral resistance associated with narrowing of its lumen.

Selective inactivation of striated muscle shortened the total urethral length to suggest that striated muscle is important to the maintenance of urethral length, *i.e.* urethral resistance and possibly urinary continence. When the external urethral sphincter was itself detached from the urethra then there followed a further decrease in urethral length and there was no response to further pudendal nerve stimulation.

These effects of surgical dissection could be compared with the effects of pharmacological destruction of striated muscle action; in the intact dog the administration of Scoline produced exactly similar changes in the profile as did surgical destruction of the striated muscle, *i.e.* shortening of the urethra with decrease in urethral resistance.

The administration of carbachol produced an increase in amplitude of the bladder neck peak with proximal displacement to indicate contraction of smooth muscle and without change in the mid-urethral resistance in the region of striated muscle. Intravenous administration of atropine which might be expected to paralyse smooth muscle failed to lower proximal urethral resistance. Intravenous administration of phenylephrine also caused an increase in bladder neck resistance without change in the overall resistance but with proximal movement of the mid-urethral peak to indicate contraction of smooth muscle.

The sub-mucosa of the urethra is richly supplied with vascular channels and it has been suggested that the normal turgor in the sub-mucosa might play a large part in the maintenance of urethral resistance at rest. Cross-clamping of the aorta was followed by a marked drop in mid-urethral resistance with return of the urethral profile to normal upon restoration of aortic flow. Cross-clamping of the inferior vena cava was followed by overall increase in urethral resistance possibly due to sub-mucosal congestion.

Urethral resistance, as measured by the urethral pressure profile technique, can be altered by many agents which affect smooth muscle, striated muscle and vascular components of urethral structure.

These studies were supported by a Grant-in-aid from the Australian Kidney Foundation.

Measurement of Residual Urine Volume using a Radioactive Tracer Technique

By D. H. KELLER, FRCS, FRACS

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Patients with neurogenic bladder disorders require special tests to assess progress towards the development of a balanced bladder. The measurement of the volume of residual urine provides valuable information.

To be of practical use a method for the assessment of residual urine must be fairly accurate and relatively simple to perform and must cause little inconvenience and be non-injurious to the patient.

A method previously described utilises an intravenous tracer dose of ^{131}I-Hippuran; 45 minutes after injection bladder activity is counted before and after micturition by the use of a flat field collimated probe. This method is acceptable provided that it is possible to position the patient accurately and to use well collimated, sensitive, manoeuvrable counting equipment.

A method has now been developed which is not dependent upon patient mobility or collimation. A small quantity of ^{125}I iodohippurate containing minimal quantities of free ^{125}I is administered intravenously. This agent is cleared by glomerular filtration and tubular secretion during its first passage through the kidneys; the mean renal transit time is 2·9 minutes. The patient is asked to void 2 hours after the injection. The residual volume in the bladder is determined by counting a small aliquot of the urine passed together with a standard of the administered radioactivity, using the principle of dilution. A probe counter can also be used to confirm the results.

An initial study was carried out on 20 patients and the results were checked by catheterisation. Subsequently a further 40 patients have been added to the group and included patients with varying degrees of impairment of renal function. In all patients 95% of the administered radioactivity was recovered at two hours after injection.

The estimated residual urine was well within 10 ml of the actual volume as determined by catheterisation.

The method has a convenience of not having to move the patient or heavy equipment and does away with errors due to probe positioning, bladder size and shape. The method is still useful despite moderate degrees of renal function. Radiation dosage to the patient is small because only 5μCi of the radiopharmaceutical is used for each measurement.

Work in the development of this technique by Drs George, Terenty and Hales in the Department of Nuclear Medicine, Royal North Shore Hospital, is gratefully acknowledged.

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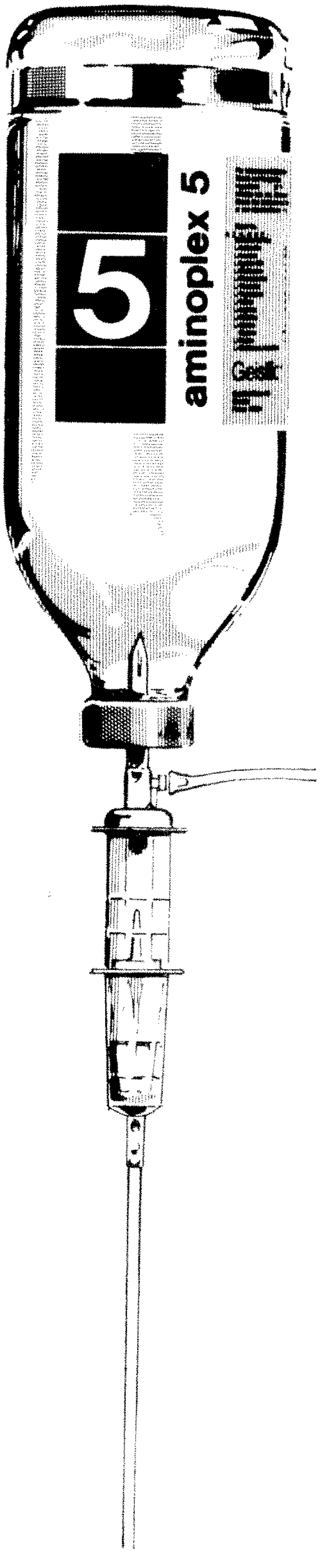

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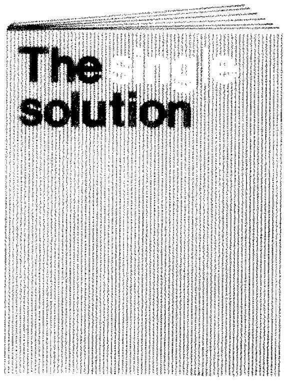

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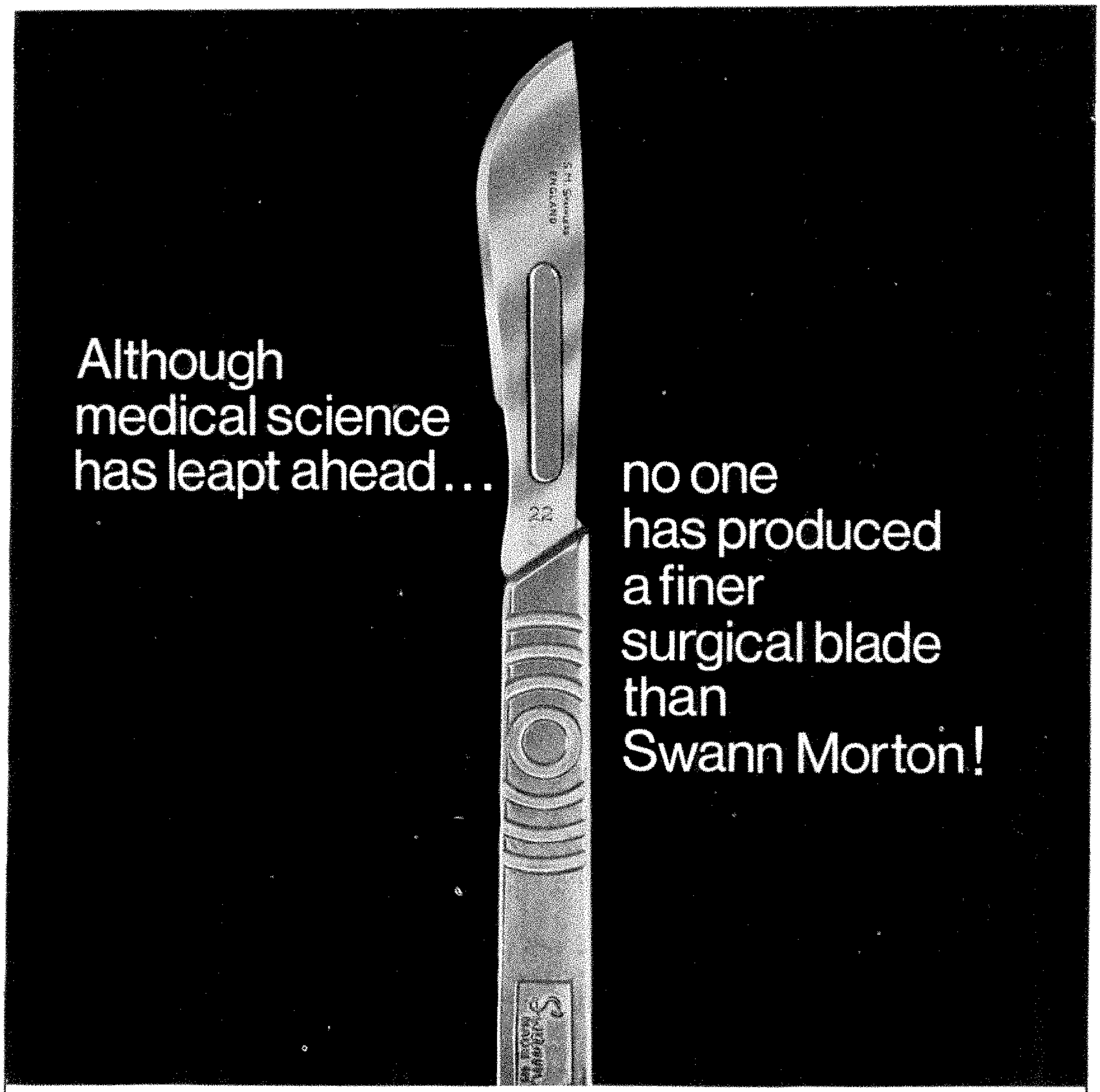

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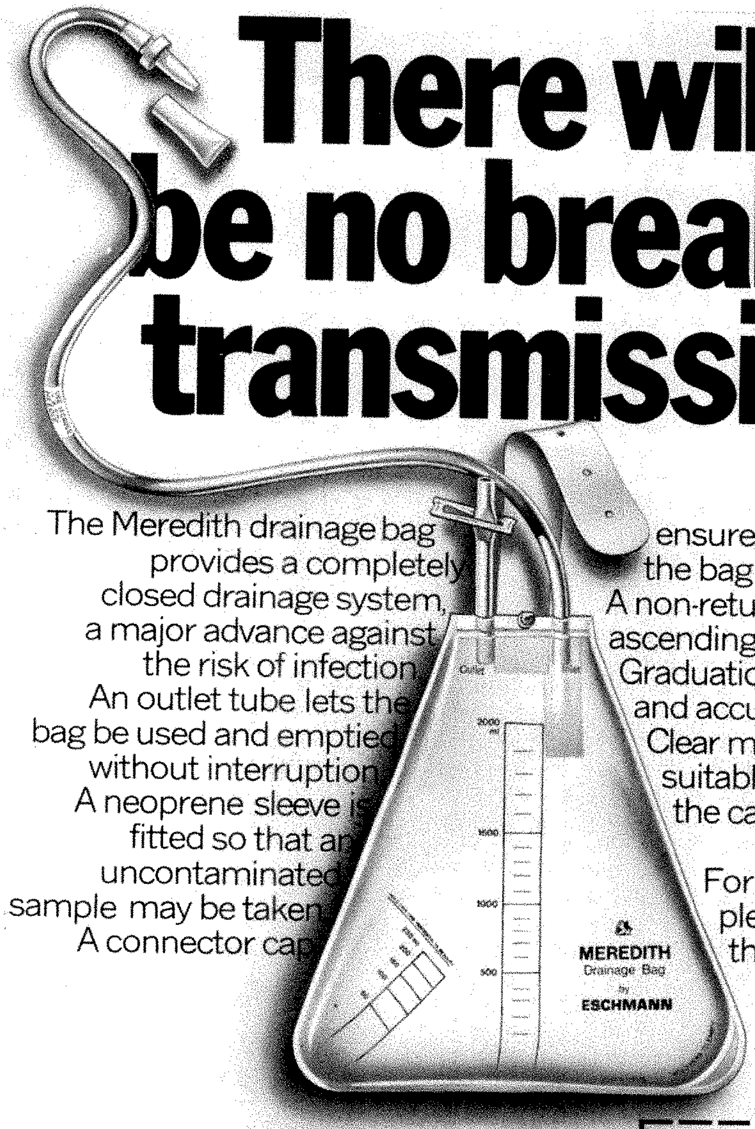

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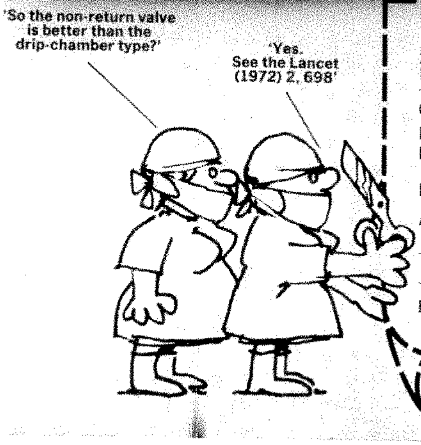
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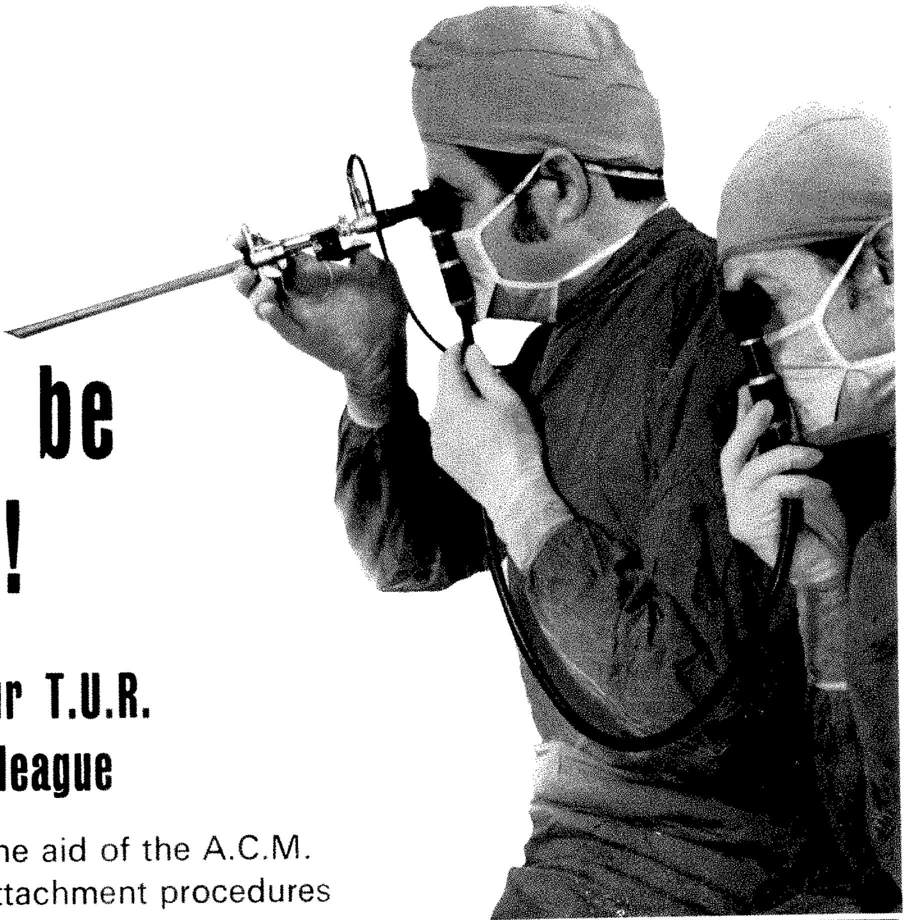

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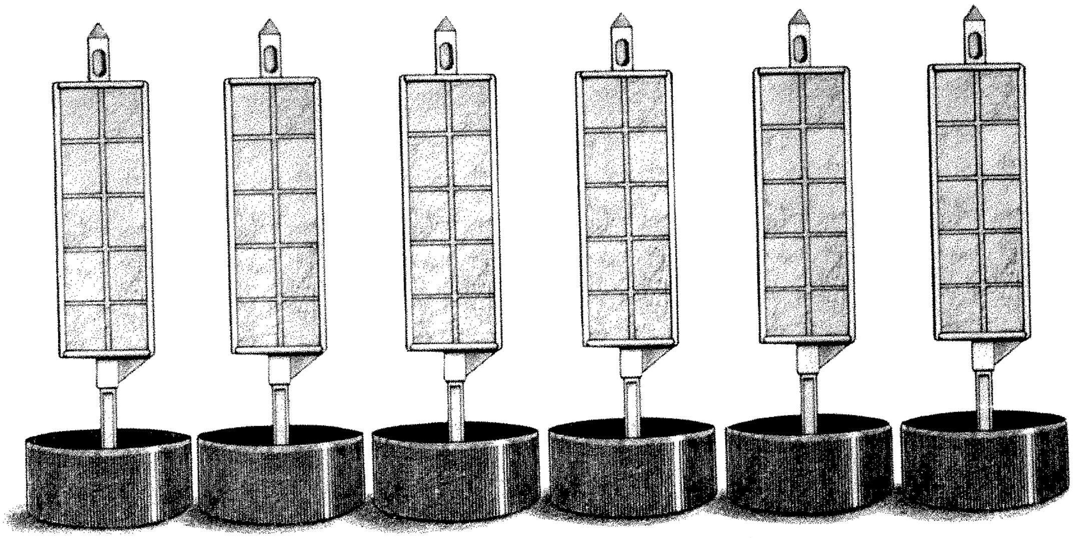

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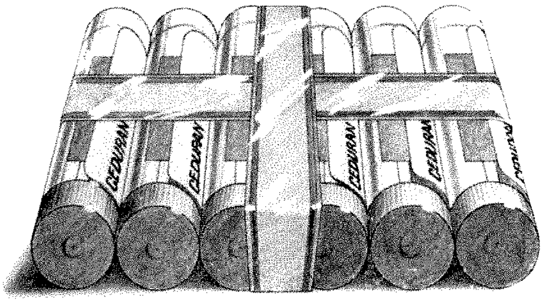

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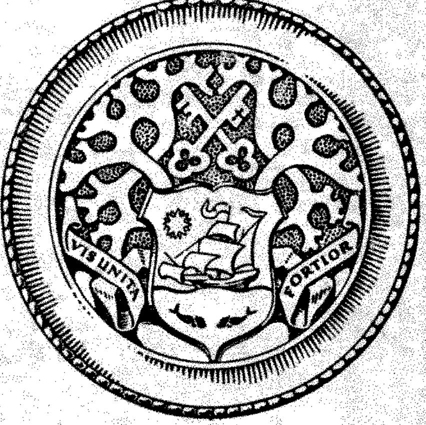

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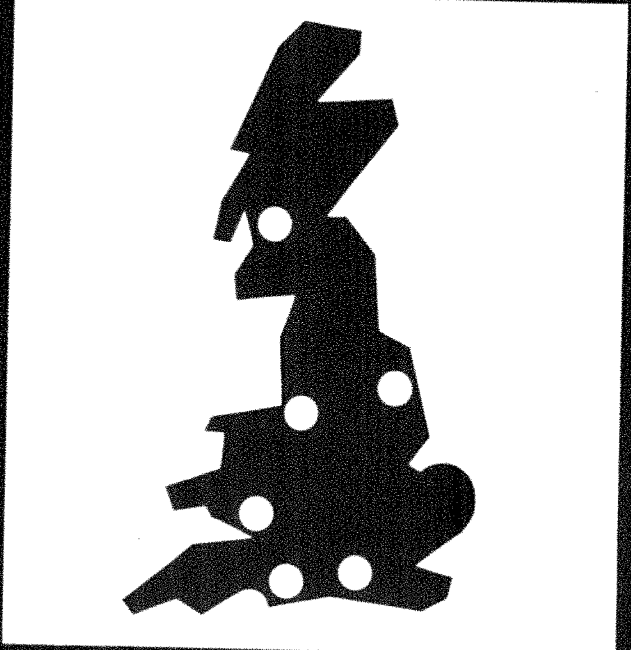

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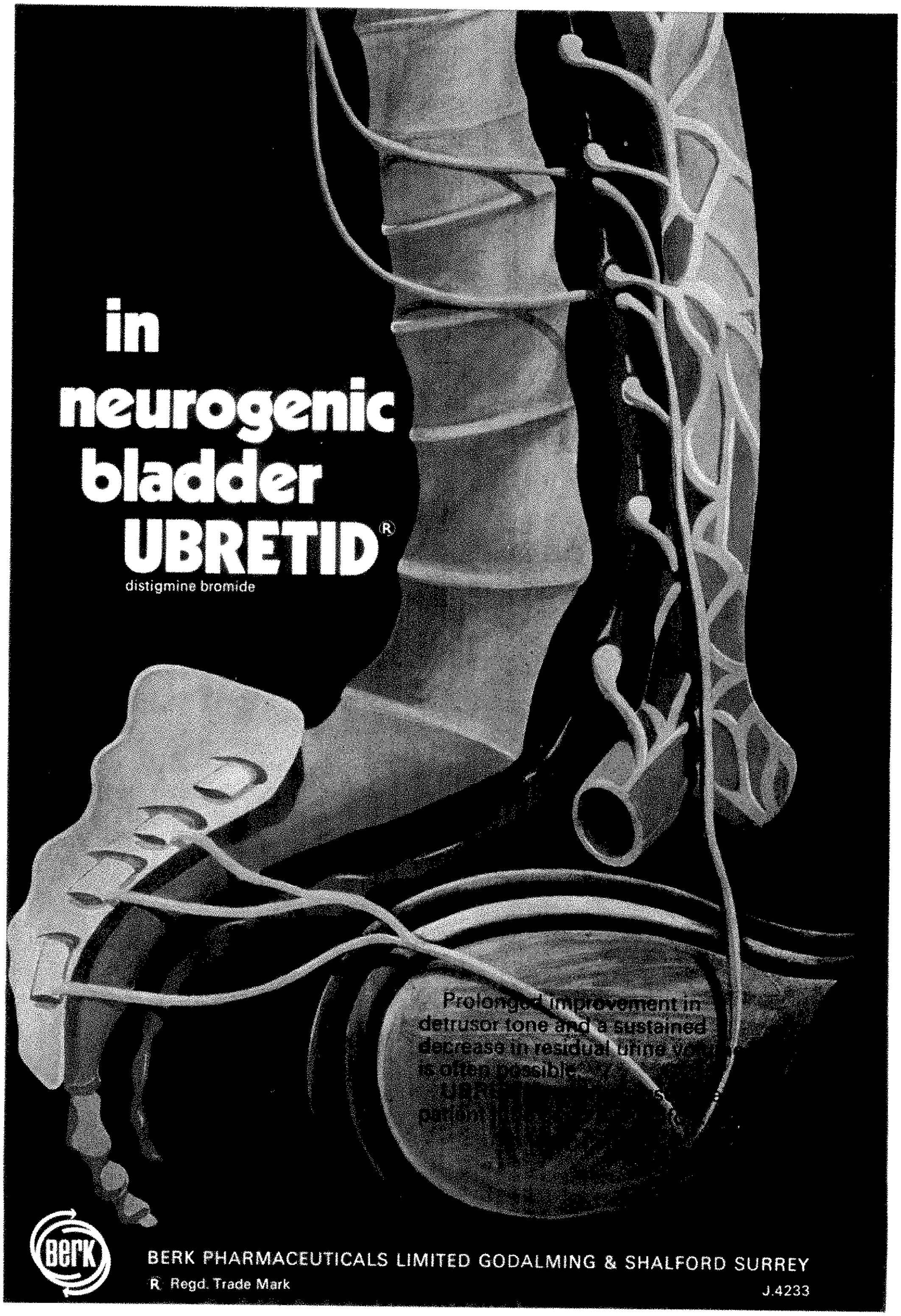

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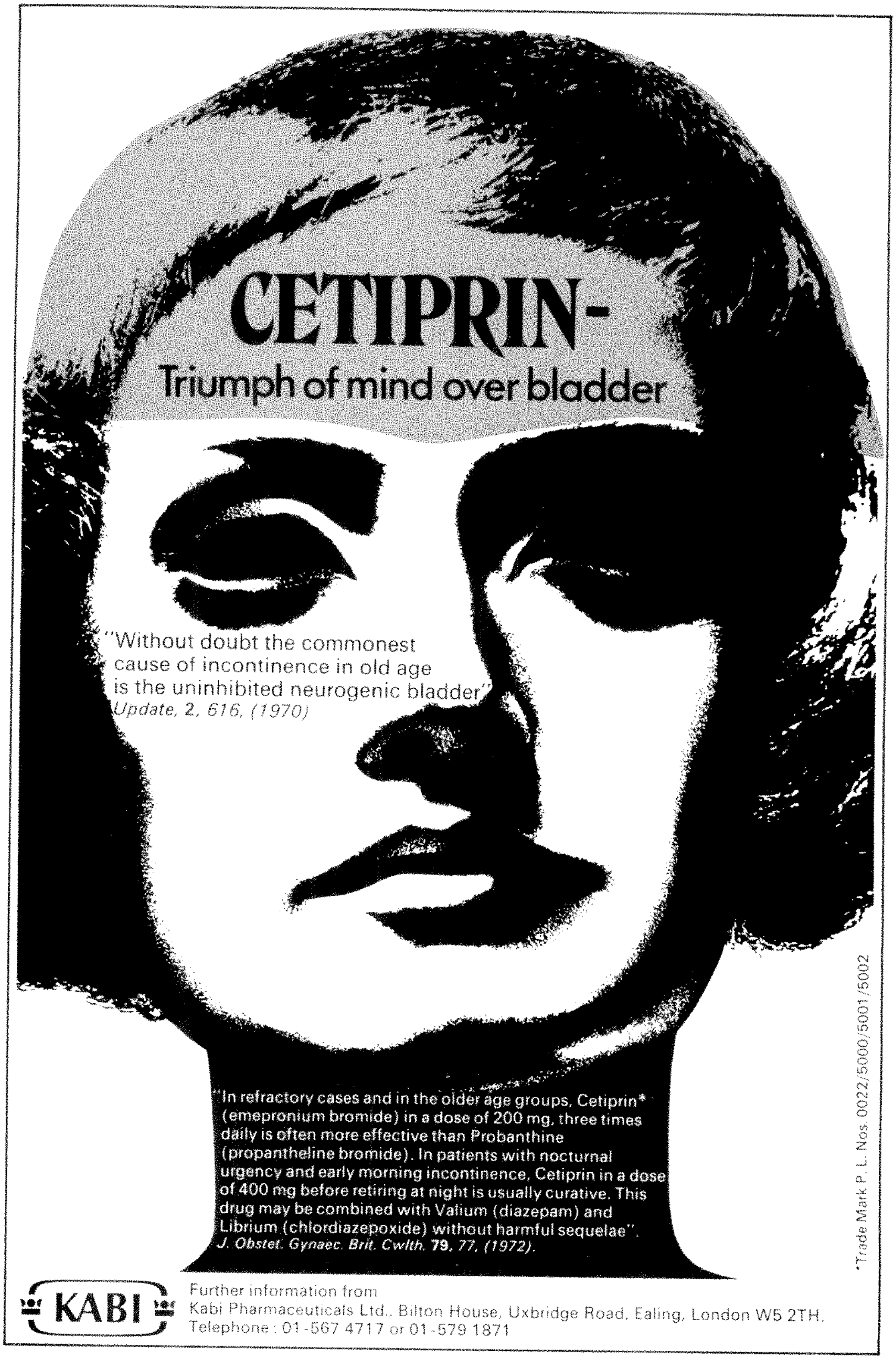

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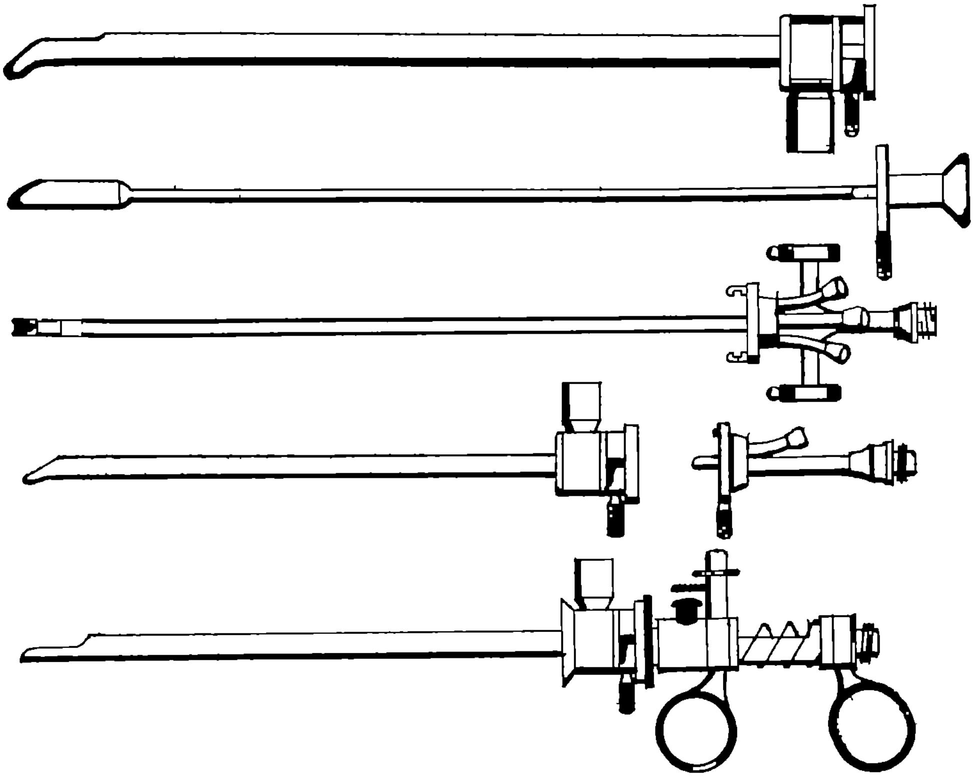

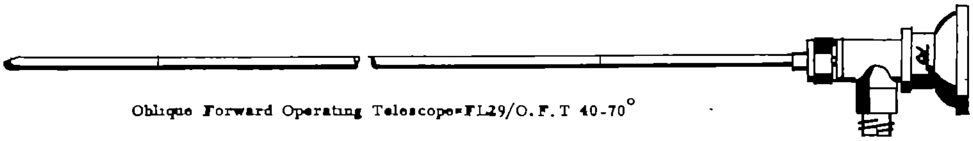

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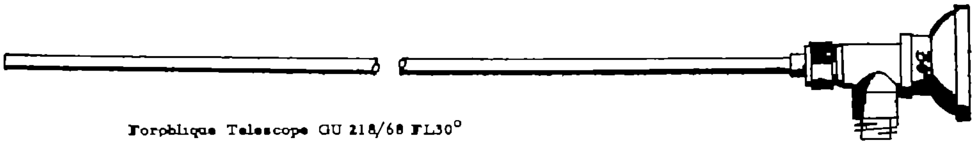

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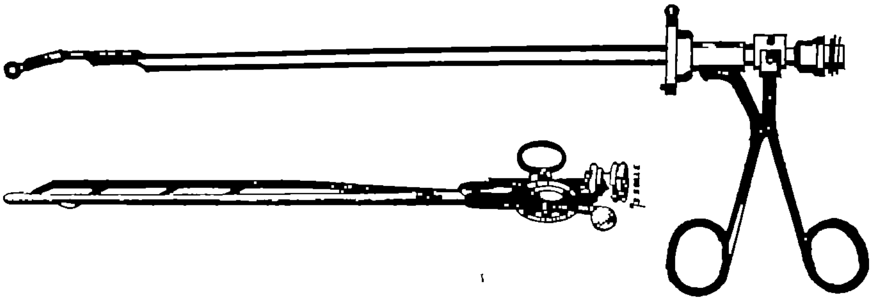

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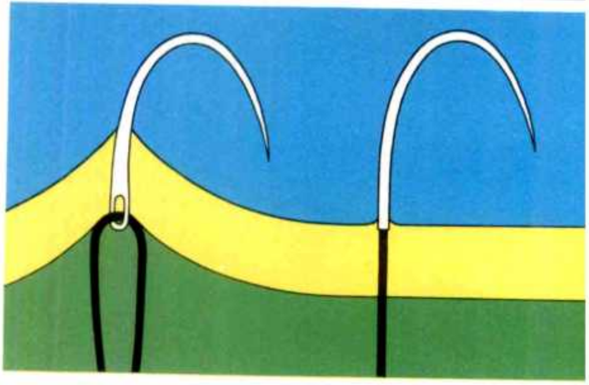

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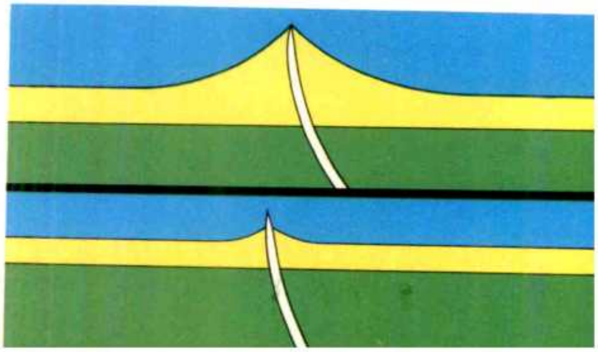

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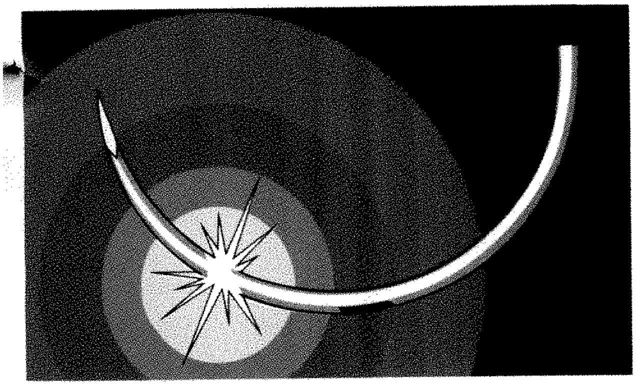

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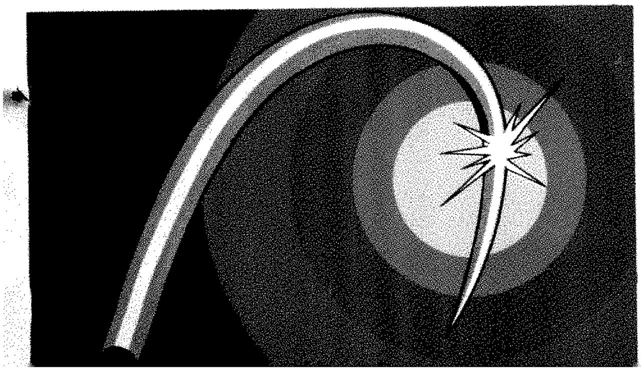

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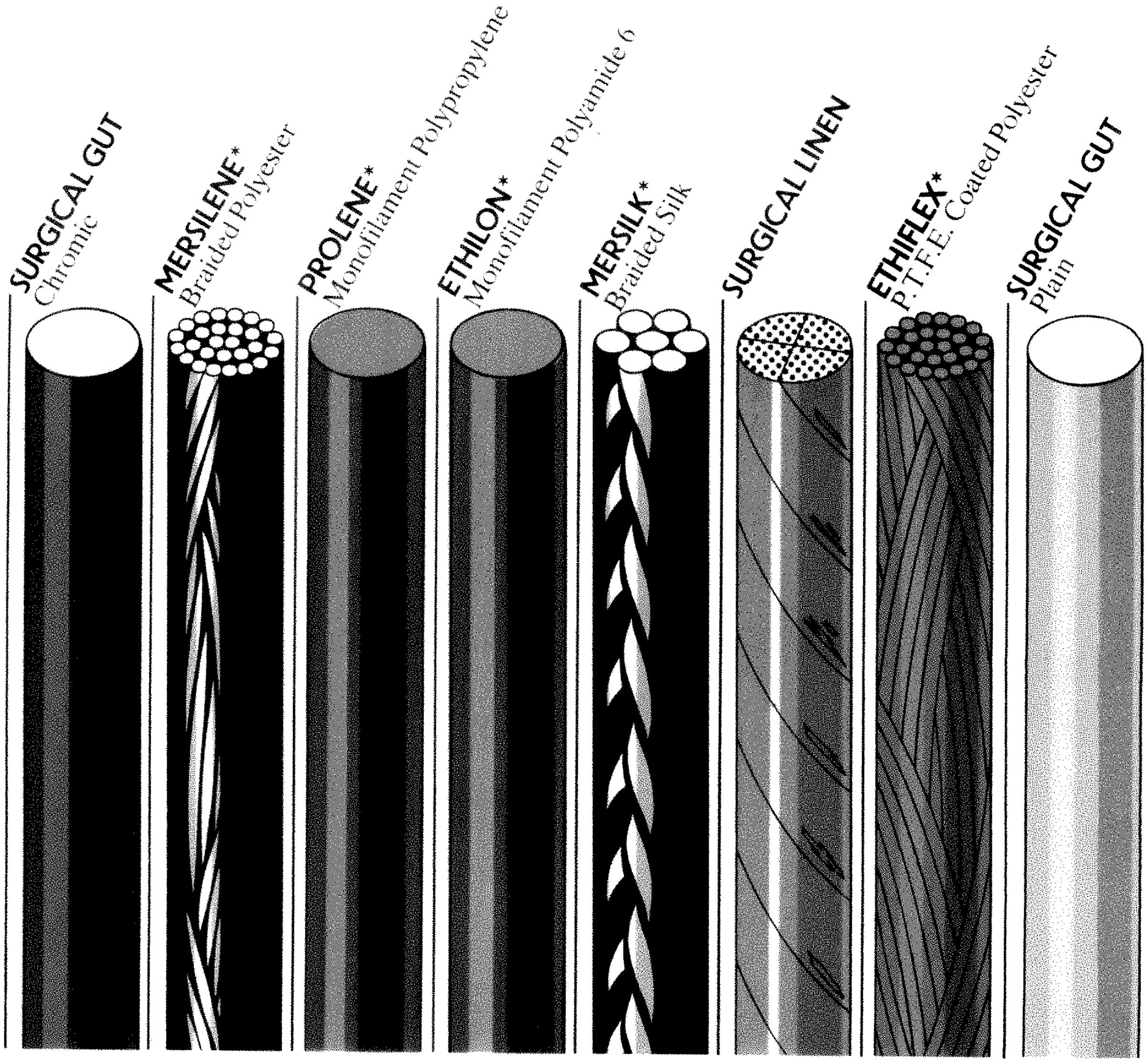

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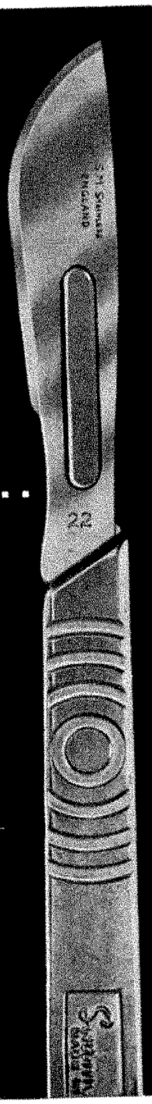

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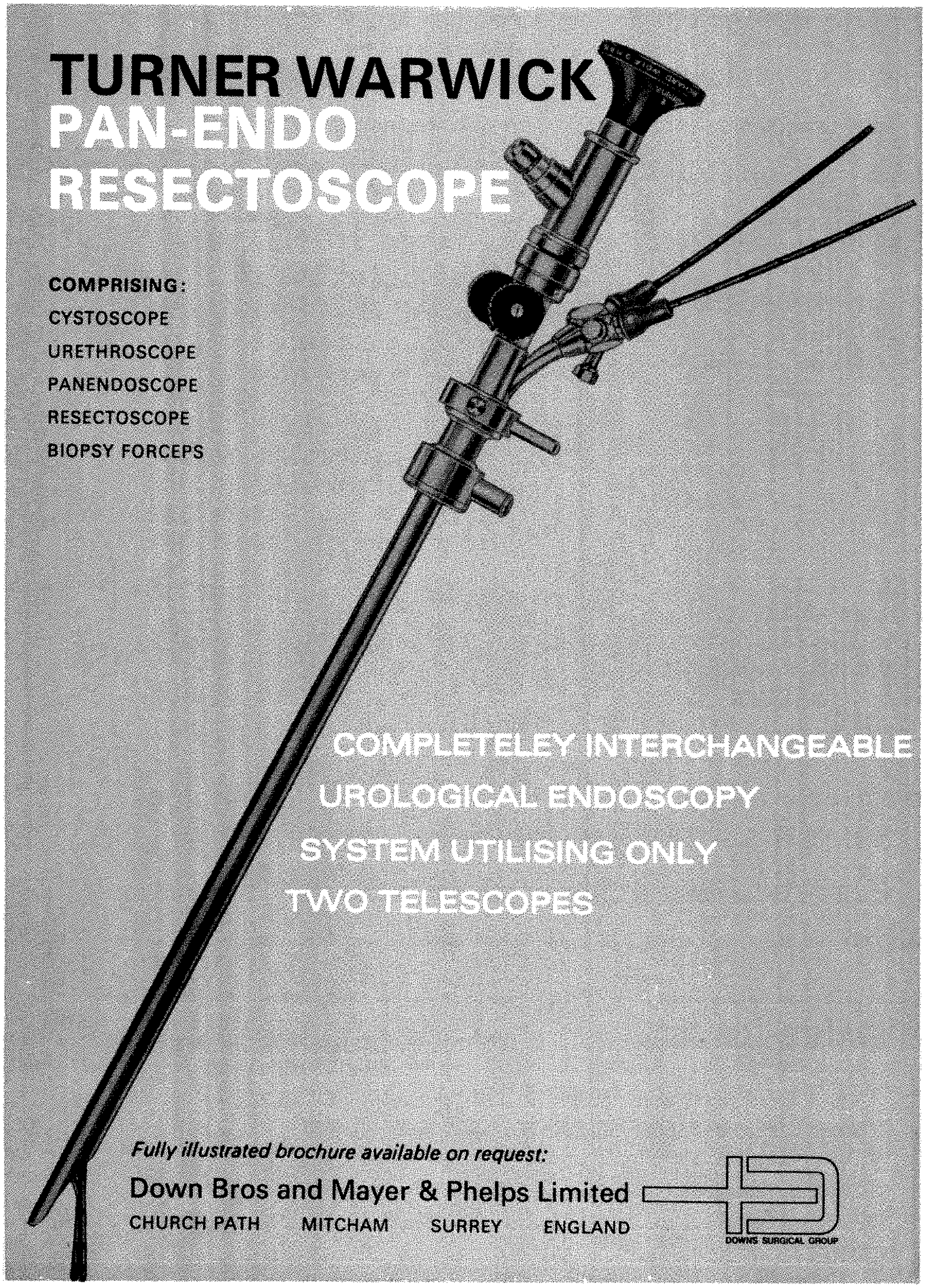

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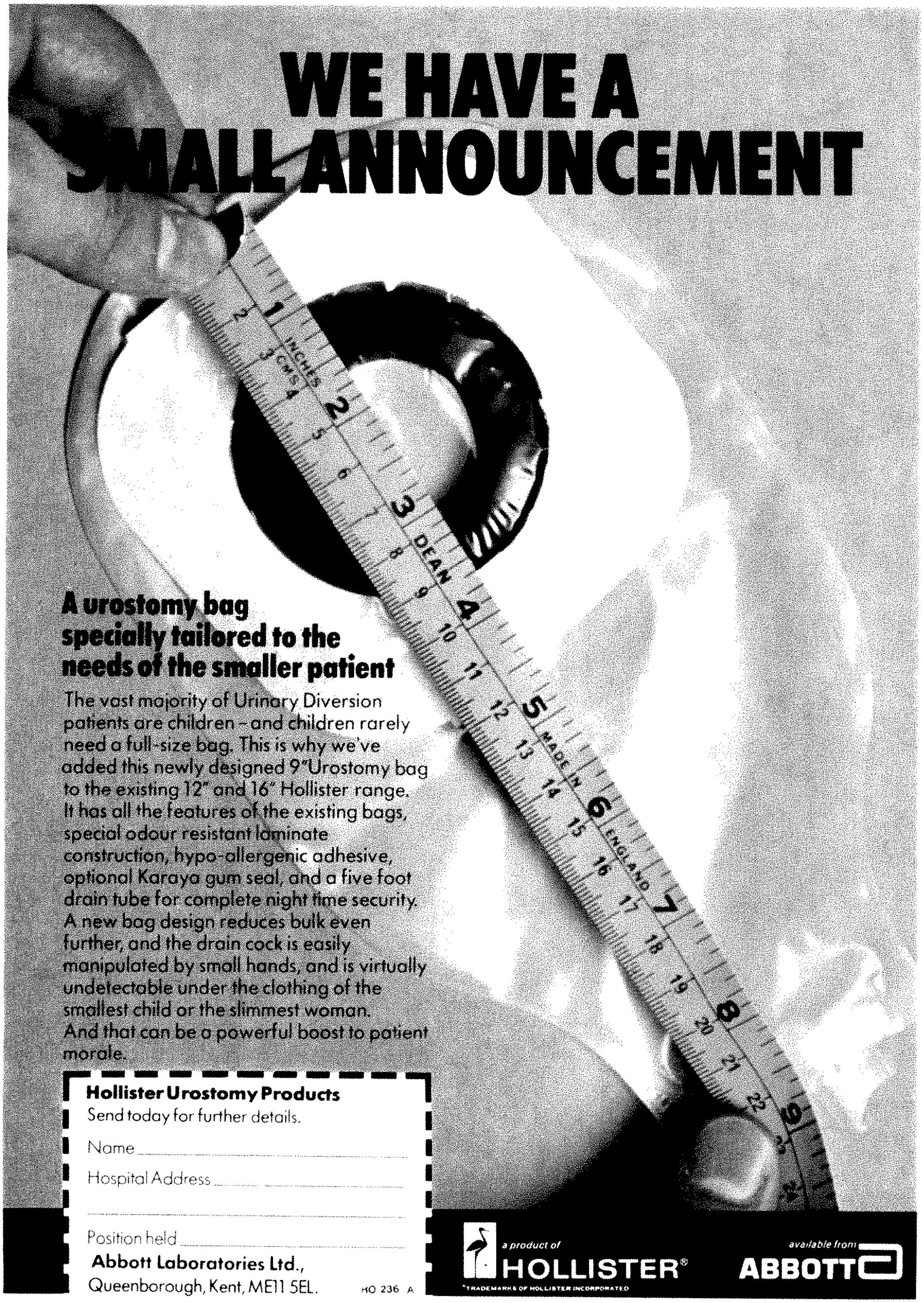

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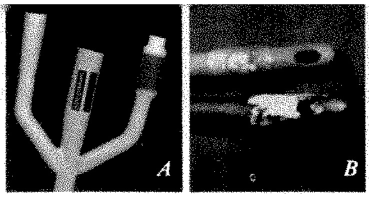

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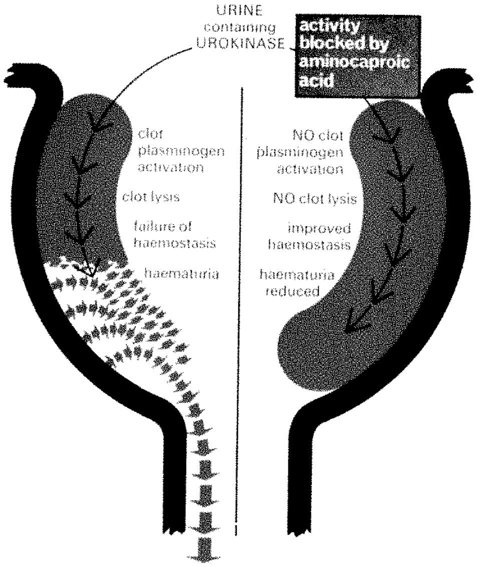

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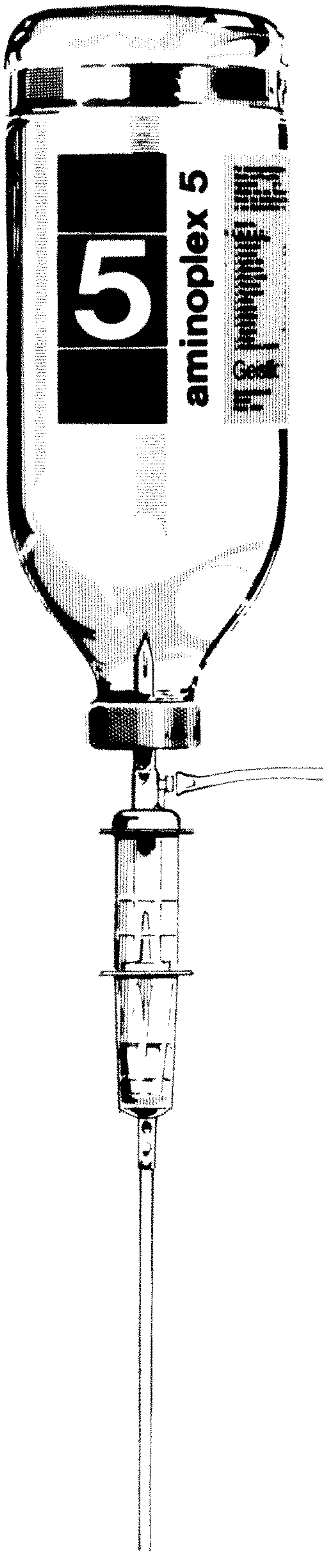

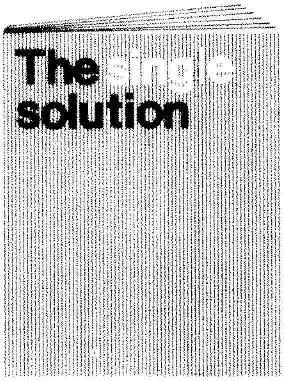
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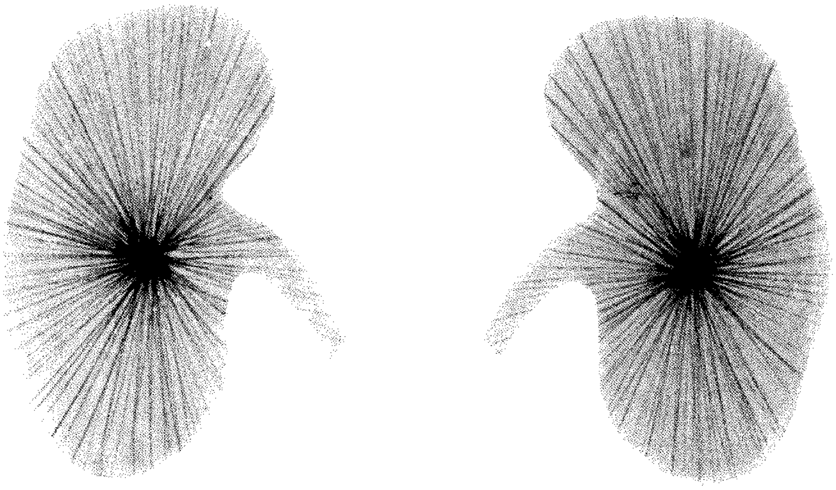

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Experimental Percutaneous Renal Infarction

ALAN R. GOLDIN, JOHAN H. NAUDE AND ROSEMARY HICKMAN

Departments of Diagnostic Radiology, Urology and Surgery, Groote Schuur Hospital and the University of Cape Town, South Africa

Interest in experimental percutaneous renal infarction was stimulated by the need for an alternative to nephrectomy in patients who were not fit for operation.

In this and the following paper experimental data on pigs and the subsequent successful therapeutic application of the method in man is presented.

Material and Method

Four young pigs weighing 15-20 kg were anaesthetised with sodium pentothal. Percutaneous catheterisation of the femoral artery was carried out using a 20 gauge Potts Cournand needle (B.D.) and preshaped polythene catheter (0·026 i.d.-0·045 o.d. Formo Cath. B.D.) with a single end hole. A control abdominal aortogram to display the anatomy of the renal arteries was

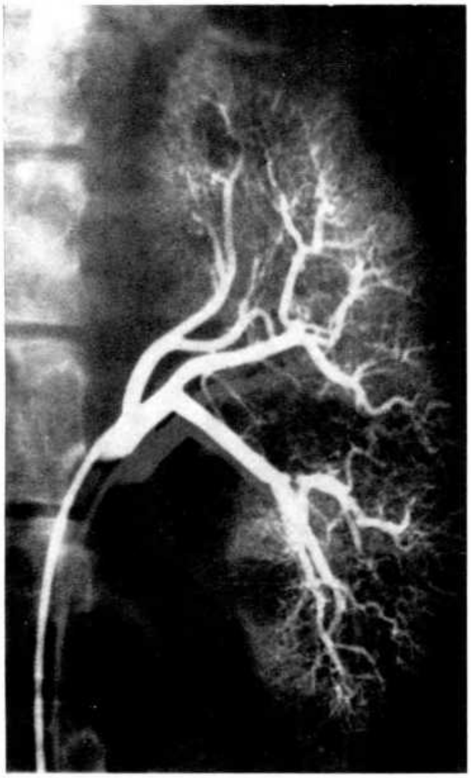

Fig. 1. X-ray of the left kidney prior to removal of the catheter. Completed injection with the entire renal vascular tree including capsular vessels packed with barium.

obtained by hand injection of 10 ml 45% sodium diatriazoate (Hypaque) and the left renal artery then selectively catheterised with the same catheter. An occluding injection of 2·5-3·5 ml of barium suspension (Steripaque, Damancy) was then injected using a 2 ml syringe in short bursts, taking great care not to spill contrast into the aorta. The entire renal vascular tree was filled in this manner over a period of 10 minutes and when no further "packing" of barium occurred the catheter was withdrawn (Fig. 1).

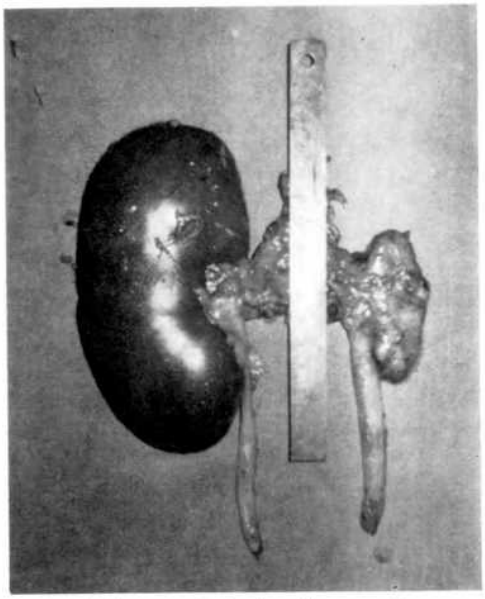

Fig. 2. 40 days post-infarction demonstrating gross shrinkage of the left and compensatory hypertrophy of the right kidney.

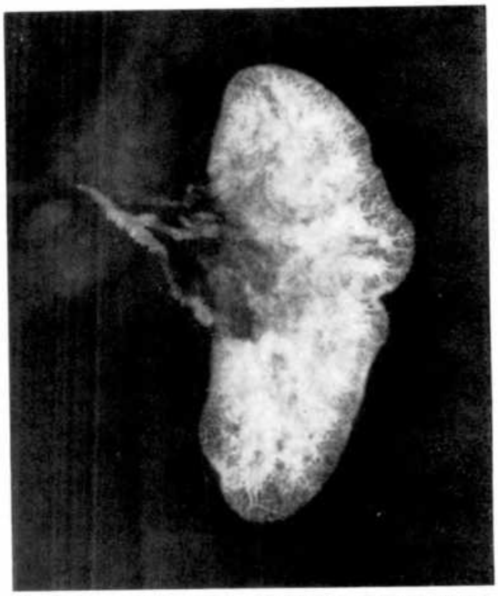

Fig. 3. X-ray of the infarcted kidney shown in Figure 2 demonstrating contracture with traces of barium in the proximal ureteric vessels and regional nodes.

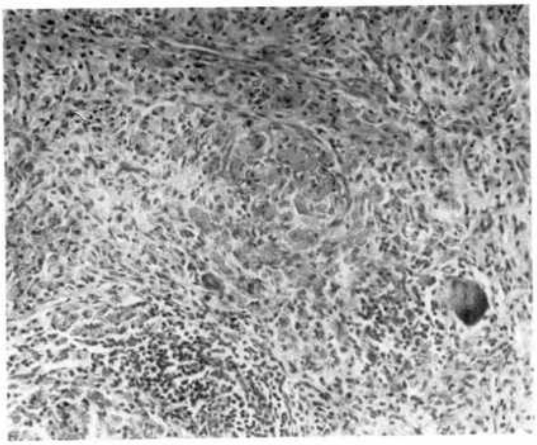

Fig. 4. Infarcted kidney showing a giant cell with histiocytes and a small collection of lymphocytes. Haematoxylin and eosin. × 100.

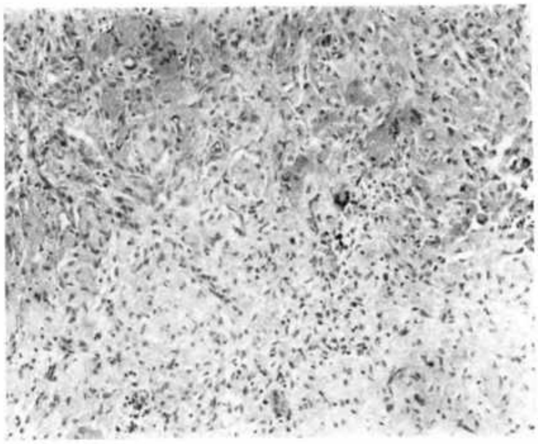

Fig. 5. Low power view of infarcted kidney with no surviving parenchyma demonstrating giant cell reaction and histiocytic response. The barium does not photograph clearly at normal luminosity. Haematoxylin and eosin. × 40.

After infarction the pigs were observed for signs of paraplegia and 37-48 days later the kidneys were removed with their regional lymph nodes and vascular connections.

Mean blood pressure was recorded before infarction and nephrectomy. Specimens of lung were also taken for histology.

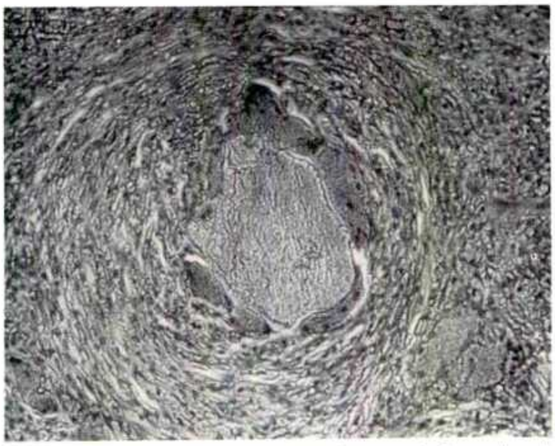

Fig. 6. A vessel containing barium photographed at reduced luminosity with refraction of the particles. There is incorporation of barium plug into fibroblastic reaction of the vessel. Haematoxylin and eosin. × 100.

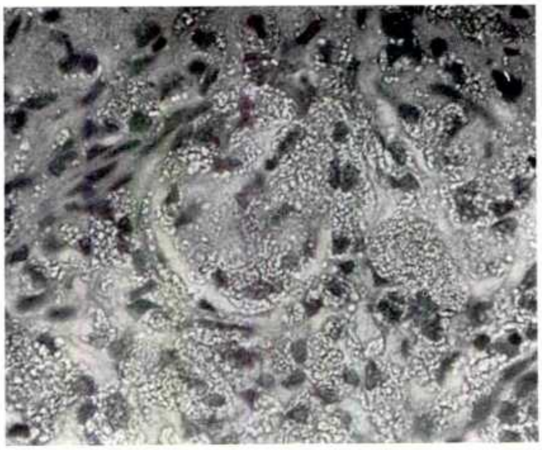

Fig. 7. A recognisable glomerulus packed with refractile barium particles. Haematoxylin and eosin. × 400.

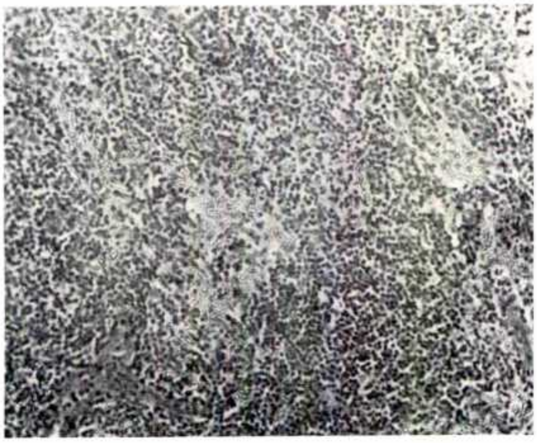

Fig. 8. Section of a regional lymph node containing a few refractile barium particles. Haematoxylin and eosin. × 100.

Results

No complications occurred and the pigs remained normotensive after the procedure.

Capsular thickening and light perinephritic adhesions were present. There was gross shrinkage of the left kidney and compensatory hypertrophy of the right in all cases (Fig. 2).

X-ray of the infarcted kidneys and regional glands (Fig. 3) demonstrated gross contracture with disorganisation of the normal vascular architecture and tiny flecks of barium in the regional nodes. Barium was also present in the proximal ureteric vessels.

Histology showed no surviving renal parenchyma and most striking was the manner in which the barium had been phagocytosed and incorporated into the cellular response. Giant cell reaction was evident (Fig. 4) and virtually the entire kidney was replaced by histiocytes and maturing fibroblasts (Fig. 5). This reaction was also present in the larger vessels containing plugs of barium (Fig. 6). The few remaining glomeruli that could be recognised contained particles of barium (Fig. 7). Histology confirmed the presence of barium in the regional nodes (Fig. 8) but there was none in the pulmonary capillaries.

The normal right kidney showed no signs of hypertension and immunofluorescent studies demonstrated no basement membrane antibodies.

Discussion

Renal artery embolisation was reported as early as 1911 by Karzner and Austin and in 1961 a variety of media were injected into rabbit renal arteries by Alexander, Heptinstall and Pickering.

Segmental renal infarction studies have been carried out by Edling and Ovenfors (1964) using blood clots and Lang (1967) using micropellets in order to assess the possible complications of renal arteriography.

However attempts at producing complete renal infarction as a potential therapeutic tool have been reported only recently. Lalli *et al.* (1969, 1971) employed Sephadex and polystyrene microspheres as occluding media in dogs but encountered an unacceptable morbidity and mortality rate due to spill of the microspheres with resultant paraplegia.

Almgard and Ljungqvist (1971), however, safely achieved adequate infarction in dogs without producing hypertension by injecting autologous muscle and glucose.

Barium was selected (Steripaque, Damancy) as the occluding agent as it satisfied the necessary criteria for occluding the vascular tree of an end organ such as the kidney. Over 90% of the particles are of the order of 1 μ in diameter according to Jackson-Moore and can reach the glomeruli. The occlusion of the small vessels is a necessary prerequisite to complete infarction which has been emphasised by Eliska (1966). Significant passage of barium through the kidney does not occur despite the small particle size providing a large enough bolus is injected to produce clumping of the particles and packing in the glomeruli. However in a tumour with multiple small arteriovenous shunts barium would be contraindicated and an alternative medium capable of occluding these relatively large vessels would be required. A further advantage of small particle size is that the mass of barium does not behave as a homogeneous foreign body and is therefore less likely to act as a nidus for infection. Phagocytosis of the particles should ultimately result in the entire mass of barium being incorporated into fibrous stroma.

The dense radio-opacity and adequate fluidity of the suspension facilitates the meticulous radiological control required for safe injection into the renal artery.

Apart from eliciting a fibroblastic response barium is non-toxic and its use in therapeutic renal infarction should not result in any untoward sequelae. This method may also find application in other areas of potential therapeutic value such as palliative adrenalectomy and an experimental model is being developed.

Shortly after completing this experimental study a patient who was a poor surgical risk but required nephrectomy for uncontrollable hypertension was presented to us. In view of the simplicity of the technique and encouraging results it was felt justified to proceed and this case is reported in the following paper.

Summary

Careful injection of barium into the renal artery of pigs produced complete infarction with no untoward sequelae. The literature is reviewed and potential application to man discussed.

We wish to thank Dr John Latham for his assistance and Professor J. H. Louw and the staff of the J. S. Marais surgical laboratory. We also thank Dr L. Werbeloff for the use of the facilities of the radiology department.

Financial support for this study was provided by the Cape Administration and the Medical Research Council. Steripaque was supplied by Damancy Co.

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British Journal of Urology (1974), **46**, 133–135

Therapeutic Percutaneous Renal Infarction

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Embolisation has been used to treat a renal arteriovenous fistula by Rizk, Atallah and Bridi (1973) but percutaneous occlusion of the renal circulation with a view to producing complete infarction has not been reported in man.[1]

Case Report

The patient treated by the technique described in the preceding paper is a 21-year-old woman who 2 years ago presented with renal failure. She has since been maintained on haemodialysis via a number of shunts and arteriovenous fistulae and is currently being dialysed via a right radial saphenous vein graft fistula.

One year ago cadaver renal transplantation was carried out and at the same operation the left kidney was removed. The histology of this kidney indicated that her renal failure was due to rapidly progressive glomerulonephritis. Hyperacute rejection of the graft occurred despite the fact that circulating antibodies had not been detected prior to the operation. However, antibodies have been consistently demonstrated subsequently.

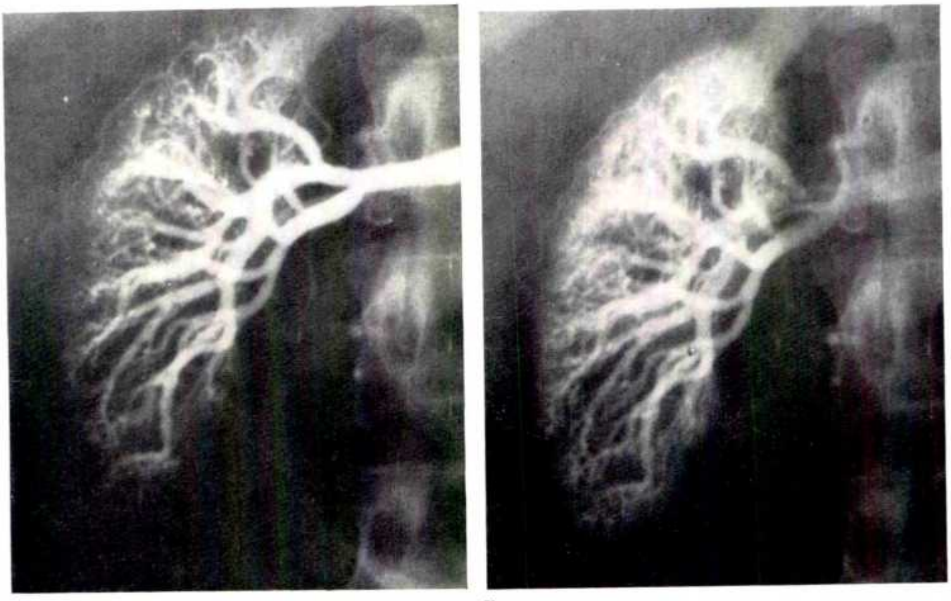

Fig. 1. A and **B**, Selective right renal arteriogram demonstrating a single renal artery and contracted kidney with a thin rim of parenchyma.

Throughout her clinical course her blood pressure has been difficult to control despite adequate medical therapy and has ranged from 240/160 to 200/120 mm Hg. The hypertension has threatened her remaining arteriovenous fistula by promoting haemorrhage after dialysis which was difficult to control.

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[1] This paper was received before the publication of the paper by Almgard and his colleagues on "The Treatment of Renal Adenocarcinoma by Embolic Occlusion of the Renal Circulation using a Suspension of Muscle" (Almgard *et al*., *British Journal of Urology*, 1973, **45**, 474-479).

Nephrectomy while desirable in this patient was felt to carry an excessive risk and she was referred for percutaneous infarction after independent opinions had considered the results of the experimental work. The patient herself fully understanding the nature of the procedure gave her consent.

The procedure was carried out under basal sedation and local anaesthesia 24 hours after discontinuing antihypertensive therapy. Preliminary abdominal aortography via a percutaneous femoral catheter confirmed the presence of a single right renal artery and this was then catheterised using a 7 French polythene Femoral Visceral 2 catheter (Cordis Co.). A selective renal arteriogram indicated that there was no adrenal artery arising from the renal and demonstrated a contracted kidney with a thin rim of parenchyma (Fig. 1).

After ensuring that the catheter was well within the renal artery 5 ml of barium suspension (Steripaque) was carefully injected intermittently under screening control using a 2 ml syringe. The patient was slightly rotated to the right side to lower the kidney.

Barium was not allowed to reflux proximal to the catheter tip at any time and the renal circulation was filled as far as the main divisions of the renal artery.

Before removing the catheter blood was vigorously aspirated to wash residual barium from the lumen thus avoiding any risk of possible spill into the aorta. The patient remained in the right oblique position for 20 minutes following the procedure and was then returned to the ward. Blood pressure readings prior to infarction were 190/120-210/120 mm Hg and remained at this level for 5 days with little fluctuation. Thereafter the blood pressure gradually dropped to 150/90 mm Hg and remained at this level.

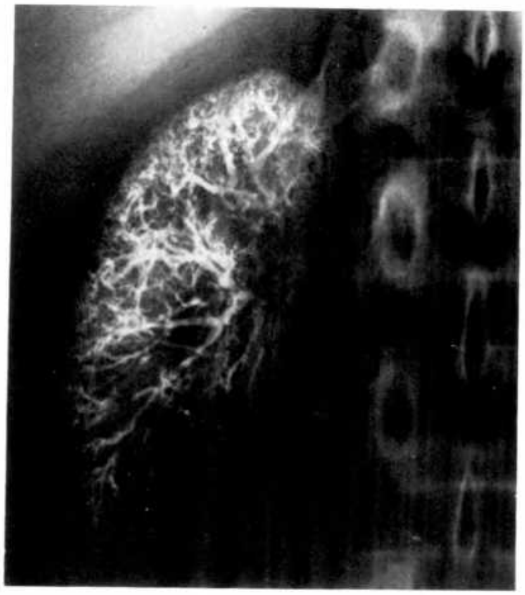

Fig. 2. X-ray of the right kidney 6 weeks post-infarction showing little shrinkage and the barium-filled vessels reduced in calibre.

The procedure was painless but right loin pain gradually developed 1 hour after infarction and was moderately severe for 3 days.

The white cell count rose from 6,000 to 17,000 on the third post-infarction day and returned to normal 10 days post-infarction.

Routine alternate day dialysis was not interrupted but in view of the risk of infection, gentamicin 80 mg was administered after each dialysis and Keflin 500 mg 6 hourly given intravenously for 5 days.

On the 10th post-infarction day the patient was discharged and it is now 8 months since the procedure was carried out. X-ray of the kidney (Fig. 2) has shown virtually no reduction in size but narrowing of the vessels has occurred compared to the pre-infarction arteriogram. This is not surprising as the kidney was contracted before infarction and little reduction in size could be expected.

Discussion

Percutaneous infarction can replace nephrectomy in selected patients where the risks of surgery are increased by uncontrolled hypertension or by hypoproteinaemia due to heavy persistent proteinuria. Renal infarction does not cause the formation of basement membrane antibodies to the normal contralateral kidney in pigs and the technique could therefore be used in prospective renal graft recipients. In such cases the interval between infarction and transplantation should be long enough for fibroblastic replacement of the kidneys to have occurred in order to reduce the risks of infection with immunosuppression. This period would be approximately 8 weeks. The risks of infection preclude the use of this technique in patients with renal failure due to obstructive uropathy or reflux.

The safety of percutaneous renal infarction depends entirely on the meticulous injection of the barium suspension into the renal artery. Great care must be exercised to prevent reflux into the aorta as this could cause paraplegia by occluding the lumbar arteries. A small volume syringe (2 ml) greatly aids injection control and barium is not allowed to reflux proximal to the catheter tip. Filling of the renal vascular tree as far as the major divisions of the renal artery results in adequate infarction and further reduces the risk of spill. For bilateral infarction requiring a change in catheters without a guide wire a sheath technique would be employed.

The pain following the procedure is probably of vascular origin and procaine perfusion of the kidney prior to infarction may reduce this.

Summary

Successful therapeutic renal infarction in a patient requiring nephrectomy is reported. The method and precautions of the technique are discussed.

We wish to thank the Superintendent of Groote Schuur Hospital, Dr J. G. Burger, for allowing us to publish this case and Professor J. H. Louw and Professor S. J. Saunders of the Departments of Surgery and Medicine for their advice and encouragement.

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Evaluation of the Xenon-133 Renal Blood Flow Method

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Although the xenon-133 (^{133}Xe) method for measuring renal blood flow has been available since 1963 (Ladefoged and Kemp, 1963), it has been employed mainly as the research tool of physiologists (Thorburn *et al.*, 1963; Ladefoged, 1968; Carriere, 1969; Carlson and Sparks, 1970) and has been used clinically by only an eclectic group of nephrologists (Lewis *et al.*, 1967; Hollenberg *et al.*, 1968, 1969). It is strange that the physician who is most intimately concerned with the vascularity of the kidney—the urologist—should not have found more use for this very valuable procedure. Experience with the technique over the past 6 years in a variety of investigative and clinical situations in Great Britain and the United States (Cosgrove, Evans and Raphael, 1968) has convinced us that it has a place in the urologist's diagnostic armamentarium.

Disturbances of renal blood flow may result in ischaemic kidneys, impairment of renal function, hypertension, fluid and electrolyte imbalance, derangement of the renin-angiotensin system (Takaku, Hirashima and Nakao, 1962) and other hormonal and metabolic disturbances. It is clearly of clinical importance to be able to quantitate renal blood flow.

In the experimental animal, renal blood flow can be measured by cannulation of the renal vein, and intrarenal distribution of the flow can be estimated by isotopic techniques such as rubidium-86 injected into the sacrificed kidney (Sapirstein, 1958).

In anaesthetised patients at open surgery, the flow in the renal artery can be measured with the electromagnetic flowmeter.

In the conscious patient the main methods used for estimating renal blood flow are variations of the para-amino hippuran clearance technique (Smith, Goldring and Chasis, 1938) which, being derived from renal function studies, are indirect indices of renal blood flow. Other methods include dye dilution techniques—such as indocyanine green (Shaldon *et al.*, 1962) which involve the simultaneous catheterisation of both renal artery and vein, and thermodilution methods (Sadler and Tuttle, 1963) which require multiple renal punctures with thermistor needles. The more familiar methods such as the renal scan, renogram and arteriogram do not quantitate flow.

These techniques all serve useful purposes. The advantages of the ^{133}Xe inert gas method in clinical practice are:

1. It is independent of glomerular and tubular function and is thus a "direct" measure of renal blood flow.
2. It can be performed on the unanaesthetised patient and also at operation.
3. The study takes only 6 minutes and can be repeated every 10 minutes.
4. No urine collection is necessary.
5. Flow is estimated in each kidney separately.
6. A numerical value of flow expressed in millilitres per gram of tissue per minute is obtained for each kidney.
7. The intrarenal distribution of nutrient flow can be estimated.

The Xenon-133 Renal Blood Flow Method

Kety and Schmidt in 1945 were the first to exploit the physical characteristics of the inert gases to quantitate organ blood flow. The theory is that if a tissue or organ can be saturated with an inert freely diffusible indicator such as ^{133}Xe, then when the indicator leaves the tissue by the veins a desaturation equilibrium is reached between the concentration of indicator in the tissue and the venous concentration. If certain physical criteria can be satisfied, then after an arterial injection of ^{133}Xe into the kidney, the rate that the xenon leaves the organ is a function of the blood flow through the kidney.

For this technique to be valid, it is assumed that recirculation of indicator is minimal and that equilibration of the injected indicator between blood and renal tissue is rapid and also that distinct zones exist within the kidney, each with its own homogeneous perfusion.

^{133}Xe in common with the other noble gases, has the property of being many times more soluble in gas than in liquid so that in one passage through the lungs, about 90% of the dose injected is excreted. This results in minimal radiation to the patient and also eliminates significant recirculation of isotope.

In practice, ^{133}Xe dissolved in saline is injected into the kidney in bolus form through a catheter placed by the Seldinger technique in the renal artery for the purpose of selective arteriography. The usual dose of xenon is 500 microcuries dissolved in 0·5 ml normal saline. This bolus is then gently flushed into the kidney with 1·5 ml of saline.

A scintillation probe, focused on the kidney, beneath the table detects the resultant gamma emissions from the xenon. The rate of desaturation of the kidney of xenon is portrayed by the washout slope on a pen recorder (Fig. 1). Analysis of this washout slope provides the means of determining renal blood flow.

When the washout slope is plotted on to semi-log paper (Fig. 2), several components of the slope are obtained either by manual or computer stripping. Analysis of the curve at 6 minutes usually yields 2 components. The numerical value of each component, the $T\frac{1}{2}$, is expressed in seconds and is the time taken for the counts to fall by 50%; the higher the $T\frac{1}{2}$ the slower the flow.

Thorburn *et al.* in 1963 using autoradiographic techniques showed that the faster component, F_1, corresponded to cortical flow. The second much slower component, F_2, probably represents medullary flow. If the $T\frac{1}{2}$ of the line through the initial slope of the washout curve is taken, an approximation of mean renal blood flow is obtained.

To convert $T\frac{1}{2}$ in seconds into flow in ml/gram of tissue/minute, the value of $T\frac{1}{2}$ for each component is incorporated into the equation.

$$\text{Flow} = \frac{\lambda \times 0{\cdot}693 \times 60}{\sigma T\frac{1}{2}}.$$

λ – the partition coefficient of ^{133}Xe in renal tissue and blood at a hematocrit of 50% is 0·7 (Ladefoged, 1966). σ – means specific gravity of the kidney tissue and blood usually taken as 1.

The formula used above was derived using Kety's theory and the Fick principle by Lassen *et al.* in 1963 for the measurement of cerebral blood flow with krypton-85. Thorburn *et al.* used a similar method with krypton-85 to study the renal circulation in dogs. Ladefoged in 1966 detailed the derivation of the equation and its application to the measurement of renal blood flow in man using ^{133}Xe.

The ^{133}Xe method thus depends on the rate of desaturation of the tissue with the injected indicator and expresses flow in millilitres of blood per gram of tissue desaturated per minute. The technique has been compared with other renal blood flow methods in the experimental animal (Ladefoged *et al.*, 1965) and the isolated perfused kidney (Cosgrove and Evans, 1968). Excellent correlations were noted between the ^{133}Xe technique and electromagnetic flowmeter recordings on the renal artery and direct measurements of flow from the renal vein.

The interpretation of the xenogram is usually best made from a series of values for each

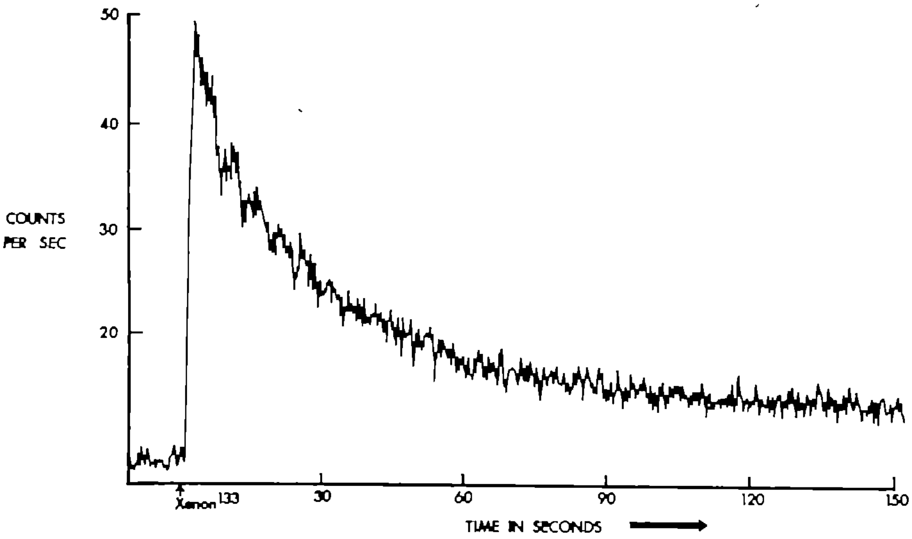

Fig. 1. ^{133}Xe washout slope from a normal kidney.

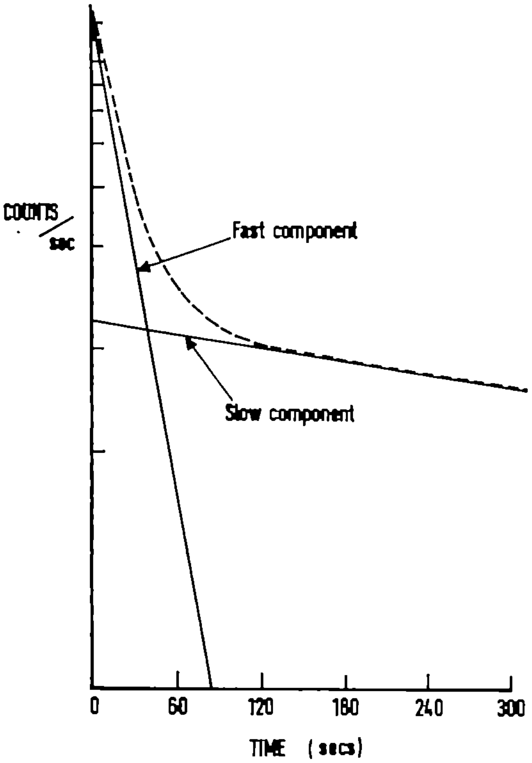

Fig. 2. Washout slope plotted on semi-log. paper. Fast component (F_1) and slow component (F_2) have been stripped off.

component (F_1, F_2, F_3) rather than from a graph, since it may not be possible to detect differences between curves with the naked eye.

The technique is an index of blood flow through perfused tissue rather than of linear flow through large vessels. It is thus a useful measure of parenchymal perfusion.

Material

Clinical Study. Using the technique described, 70 kidneys were studied in 50 urological patients. The data obtained from these studies has been analysed in an attempt to: (1) Describe the normal "renal xenogram". (2) Compare the renal xenogram with the renal arteriogram and other studies in each case, and to relate the results obtained to the clinical and pathological findings. (3) Determine the relative merits of the renal arteriogram and the renal xenogram. (4) Conclude whether or not knowledge of renal blood flow was helpful in the management of the individual case. (5) Define those urological areas, if any, where renal xenography may be of value.

Results

1. *The Normal* ^{133}*Xe Renal Blood Flow Profile*

From a study of 25 kidneys displaying normal function and a normal arteriogram, a standard pattern for the renal xenogram emerged (Table—Patient T. J.).

These features are: (*a*) A semi-log plot, which over 5 minutes separates readily into 2 components (Figs. 1 and 2). (*b*) A faster component (F_1) accounting for more than 70% of the total counts with a flow value of more than 2 ml/g/min. (*c*) A slower component (F_2) accounting for 30% or less, of the counts with an extremely variable value. (*d*) A mean blood flow (F_m) with a value about 80% of F_1.

In the normal kidney, it is probably correct to term the faster component cortical flow and the slower component medullary flow. In the normal kidney, as the mean blood flow (F_m) obtained from the initial slope bears a constant relationship to cortical flow (Cosgrove, Evans and Raphael, 1968), the need for curve analysis may be obviated.

2. *The Abnormal* ^{133}*Xe Renal Blood Flow Profile*

In the pathological kidney many deviations from the normal pattern are seen. The washout slope itself may appear grossly abnormal. The semi-log plot may reveal more or fewer than the 2 usual components. The flow values of each component may be abnormal, and the per cent distribution of ^{133}Xe in the compartments of the kidney may vary from the usual range. Mean blood flow no longer bears a constant relation to cortical flow.

(a) *Renal Mass Lesions*

Benign renal cysts have normal ^{133}Xe renal blood flow profiles as shown in patient T. O. In renal carcinoma there may be an increase in blood flow, particularly in vascular tumours. Alteration in the compartmental distribution of xenon can occur when the renal architecture is grossly deranged. Frequently, however, as shown in patient I. C. the pattern is normal in every way. It is fair to anticipate in the presence of renal carcinoma that if the xenogram is normal, then the main renal vein is patent. In this patient's case, this fact was confirmed at operation.

Another patient, P. G., with renal cell carcinoma had a washout slope suggestive of renal vein occlusion in that the slope did not come down anywhere near the baseline at 6 minutes. At surgery the main renal vein was found to be obstructed by invading tumour.

(b) *Renal Vascular Disease*

The combination of the arteriogram with the xenogram has been most fruitful in evaluating cases of renal artery stenosis, renal arterio-venous fistula and renal vein thrombosis.

We have shown in an experimental study (unpublished) that the xenon technique cannot delineate areas of totally infarcted kidney, nor can it pick up branch occlusions of the renal vessels. However, renal ischaemia can be demonstrated in significant stenosis of the main renal artery.

Patient M. C. had an ischaemic kidney due to extrinsic compression of the main renal artery by a retro-peritoneal tumour. There is uniform reduction in all components of renal flow.

Table

^{133}Xe Renal Blood Flow Profiles in 22 Patients

Patient			Flow in ml/g/min				% Isotope Distribution			
Name	No.	Diagnosis	$F_{(m)}$	F_1	F_2	F_3	C_1	C_2	C_3	Comment
T. J.	35	Normal kidney.	5 5	6·0	1·8	...	80	20	...	Normal flow profile.
T. O.	25	Renal cyst.	3 0	3·0	0 33	...	96	4	...	Normal flow profile.
I. C.	27	Renal carcinoma.	4·0	5·4	0·3	...	85	15	...	Normal flow profile.
P. G.	5	Renal carcinoma.	3·0	3·6	0·26	...	56	44	...	Parenchymal disturbance. Curve stays high.
M. C.	7	Ischaemic kidney.	1·02	1·38	0·11	...	76	24	...	Ischaemic flow profile.
A. G.	22	Repaired R.A.S.	3·0	3·75	0·6	...	77	23	...	Normal flow profile.
J. D.	23	Hypertension. Abnormal scan.	1·4	2·0	0·3	...	65	35	...	Low normal flow. ? Mild parenchymal disturbance.
J. D.	23	Hypertension. Normal scan.	3·0	4·0	0·5	...	88	12	...	Normal flow profile.
E. S.	24	Asymptomatic F.M.H.	2·7	2·7	0·33	...	93	7	...	Normal flow profile.
W. W.	45	Renal A-V fistula. Pre-operation	3 07	5·0	2·0	0·22	50	40	10	Extra fast component.
W. W.	45	A-V fistula repaired.	1·04	2·5	0·14	...	75	25	...	Normal flow profile.
W. M.	20	Renal vein thrombosis.	0·46	0·46	...	...	...	...	...	Slow unicomponent flow. Curve stays high.
O. P.	26	Glomerulo-nephritis.	2·0	3·75	1·0	0·3	54	35	11	Normal flow. Parenchymal disturbance.
F. S.	32	Hypertension. Chronic pyelonephritis.	1·5	2 0	0·11	0 02	65	25	10	Low normal flow. ? Mild parenchymal disturbance.
S. W.	46	Staghorn calculus. Non-functioning kidney.	0·5	1·11	0·05	...	42	58	...	Marked ischaemia and parenchymal disturbance.
S. W.	46	"Normal kidney"	1·04	2·5	0·1	...	65	35	...	Normal flow but mild parenchymal disturbance.
M. B.	47	Obstructed ureter. Non-functioning kidney.	1·5	3·0	0·25	...	58	42	...	Normal flow. Moderate parenchymal disturbance.
M. B.	47	"Normal kidney"	3·0	3·3	0·27	...	82	18	...	Normal flow profile.
M. C.	18	Renal trauma.	3·0	3·75	0·4	...	75	25	...	Normal flow profile.
R. T.	34	? Transplant rejection.	0·67	0·86	0·04	...	75	25	...	Ischaemic kidney.
R. S.	37	? Transplant rejection.	2·5	2·5	...	...	...	...	...	Single flow component.
F. E.	36	? Transplant rejection.	1·9	6·0	0·1	...	65	35	...	Good flow, mild parenchymal disturbance.

Patient A. G., who previously had hypertension and renal artery stenosis, now has a normal flow profile following renal re-vascularization surgery. At the time that this study was performed the patient was normotensive.

Of considerable interest are borderline cases such as patient J. D., who was investigated for hypertension and found to have an abnormal renal scan on the left side but a normal arteriogram. The contralateral kidney appeared normal in every way. The xenogram on the left showed a more ischaemic pattern than on the right. The level of ischaemia was the lower limit of normal.

Selective renal vein renin estimations were not helpful in localizing an ischaemic kidney. This patient will be followed to determine whether more overt ischaemia develops in the left kidney.

In contrast, patient E. S., who was normotensive, had the arteriogram performed for other reasons and was found to have bilateral fibro-muscular hyperplasia (Fig. 3). The xenogram was, however, normal.

These findings further confirm the well-known fact that the radiologic appearance of arterial narrowing is not always associated with renal ischaemia. Furthermore, renal ischaemia can exist in the presence of an apparently normal arteriogram.

An unusual case (W. W.) of renal arterio-venous fistula was studied. The flow profile showed an extra very fast component, presumably due to the A-V shunting. The patient was normotensive. Conservative renal surgery was undertaken with ligation of the branch artery supplying the fistula with good clinical and radiological results. The xenogram returned to the normal 2 component pattern after operation.

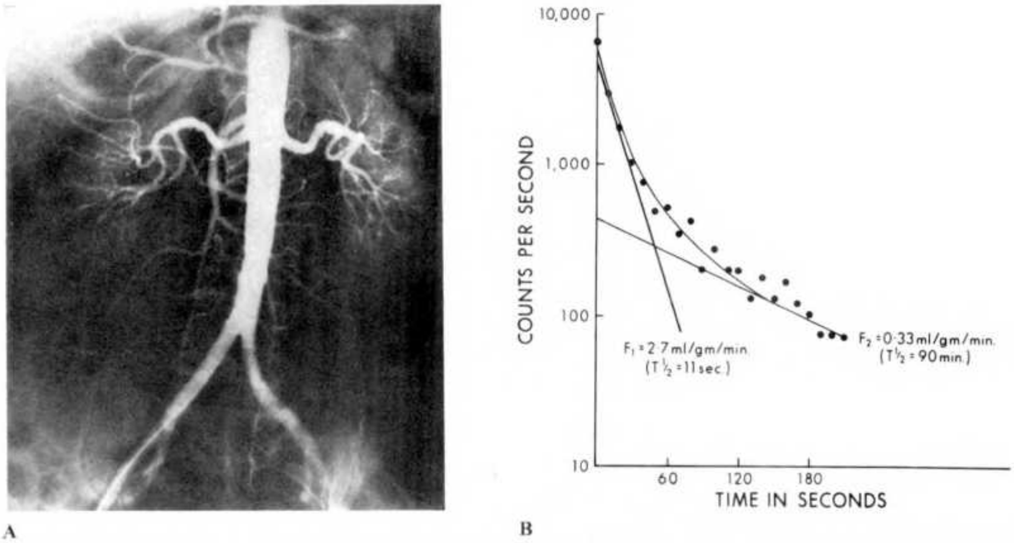

Fig. 3. Patient E. S. A, Arteriogram showing bilateral fibromuscular hyperplasia of the renal arteries. B, Left xenogram showing fast (F_1) and slow (F_2) components; flow for each component is expressed in ml/gm/min.

When the main renal vein is occluded, as has already been described with reference to renal carcinoma, the xenogram is grossly abnormal. The isotope cannot leave the kidney so the slope does not come down.

W. M. was a young hypertensive male who presented with oedema, proteinuria and a history of right flank pain. The renal arteriogram was unremarkable. The xenogram on the right side was, however, most unusual. The washout slope did not fall and was furthermore not separable into components. This was taken to indicate renal vein occlusion and this was subsequently confirmed by renal venography.

(c) *Renal Parenchymal Disease—Medical*

This field has been extensively covered by other investigators (Ladefoged, 1968; Hollenberg *et al.*, 1968, 1969) and the present studies are confined to those cases which may have required urological procedures.

A young lady (O. P.) gave a history of proteinuria and oedema and was suspected of having renal vein thrombosis. The pattern of the xenogram, however, was unlike that described for renal vein thrombosis, as it showed 3 components—1 fast, and 2 slow ones with abnormal intrarenal distribution of xenon. The arteriogram and venogram were both normal and the diagnosis was found to be proliferative glomerulo-nephritis.

Patient F. S. was a 49-year-old Negro female with a 5-year history of hypertension. She underwent renal arteriography because of an abnormal intravenous urogram and was found to have a small pyelonephritic left kidney, the right kidney being normal. The blood flow profile on the left side was only minimally abnormal—the cortical flow of 2 ml/g/min is the lower limit of normal. It was felt that as the kidney was not significantly ischaemic in terms of flow per gram of tissue, it was unlikely that the patient's hypertension would respond to nephrectomy. This proved to be the case as the blood pressure remained elevated after removal of the kidney.

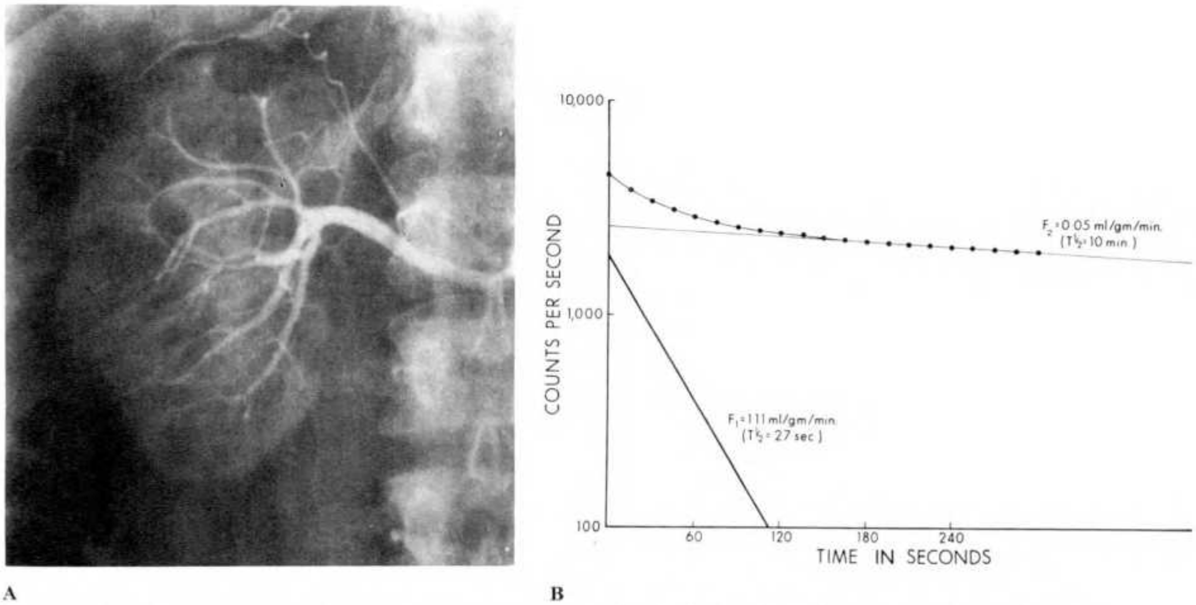

Fig. 4. Patient S. W. **A**, Right renal arteriogram showing marked ischaemic changes. **B**, Right xenogram showing fast (F_1) and slow (F_2) components; flow for each component is expressed in ml/g/min.

(d) *Renal Parenchymal Disease—Surgical*

These cases are of particular interest to the urologist as a blood flow profile in the obstructed or calculus containing non-functioning kidney may possibly enable him to forecast whether or not the kidney is salvageable.

S. W., a man of 62 with moderate elevation of the BUN and serum creatinine, had a non-functioning right kidney containing a branching calculus. The blood flow study of the right side confirmed the angiographic appearances (Fig. 4) of an ischaemic kidney—the result of long-standing pyelonephritis and calculus disease. At surgery the kidney was found to be unsalvageable. Despite normal pyelographic and angiographic appearances of the left kidney, the flow profile displayed a slightly abnormal distribution pattern of xenon. This may be related to the elevated BUN, and it is possible that the xenogram can detect early evidence of renal parenchymal disease.

Patient M. B. developed unilateral ureteral obstruction with loss of renal function following uretero-ileo-cutaneostomy. There was radiologic evidence of complete ureteral obstruction and non-function of the left kidney for more than 6 months. The xenogram, however, displayed a good flow profile on the affected side. At surgery, the kidney was found to have healthy parenchyma and was conserved. One week following ureteral disobliteration, the kidney resumed excretion of contrast. In this case, the xenogram proved helpful in predicting recovery of function in a non-functioning kidney.

(e) *Renal Trauma*

There is much controversy among urologists on the subject of whether or not to operate to attempt to salvage part of a traumatised kidney, and if so, when? (Scott, Carlton and Goldman, 1969; Morrow and Mendez, 1970). The renal xenogram may be of value in this situation in describing the vasculature and hence the viability of the damaged kidney.

A young man (M. C.) suffered blunt trauma to the left kidney. Intravenous urography demonstrated non-function of the lower pole of the kidney and extravasation of contrast outside the kidney. In spite of conservative management for 2 weeks, his clinical condition did not stabilise and haematuria and flank pain persisted. Renal xenography demonstrated a normal flow profile, indicating that the upper pole of the kidney was worth salvaging. This was confirmed by an arteriogram. The patient underwent successful lower pole partial nephrectomy and made an excellent recovery. In this instance, the xenogram did no more than confirm the arteriographic findings.

(f) *Renal Transplant Rejection*

As it is generally believed that the early phase of the rejection phenomenon entails a vascular process, it seemed logical to determine how effective the renal xenogram is in the difficult process of evaluating possible rejection in kidney transplant patients. Lewis *et al.* (1967) have done studies which indicate that the ^{133}Xe technique can be useful in diagnosing early rejection.

Three patients suspected on clinical grounds of rejecting transplants that had been functioning for more than 3 years were studied.

In patient R. T., the renal arteriogram showed normal large and small vessels to the kidney. The ^{133}Xe blood flow profile was abnormal, with a markedly ischaemic pattern. The patient progressively deteriorated and rapidly rejected the kidney.

The second patient (R. S.) had problems with his renal transplant ever since its insertion. He was admitted for investigation of sudden deterioration in renal function. The arteriogram showed appearances similar to the first case—rather non-specific. The renal xenogram was abnormal, in that the slope could not be broken down into components (Fig. 5). However, there was no gross ischaemia. The patient slowly deteriorated and 3 months later required dialysis because of rejection. Perhaps in the second case the rejection process was picked up early—before ischaemia became a feature. In both cases there were marked changes in the xenogram without corresponding arteriographic changes.

The third renal transplant case, F. S., was admitted for evaluation of general malaise, fever and impaired renal function. In this patient the arteriogram looked abnormal with spastic large branches and possible small vessel disease peripherally. The renal xenogram in this patient was virtually normal (Fig. 6). The diagnosis in this strange case turned out to be toxoplasmosis. The patient did not reject the kidney and both she and her kidney are doing well 2 years after the episode.

It appears from this limited study of late rejection that the ^{133}Xe renal blood flow profile is of value in confirmation of the diagnosis. It is suggested that true rejection must be unusual in the presence of a normal renal xenogram.

Discussion

The renal xenogram has not by itself saved any lives. However, the technique has not caused any morbidity or adverse effects in the 50 patients studied in this series. Only those patients who

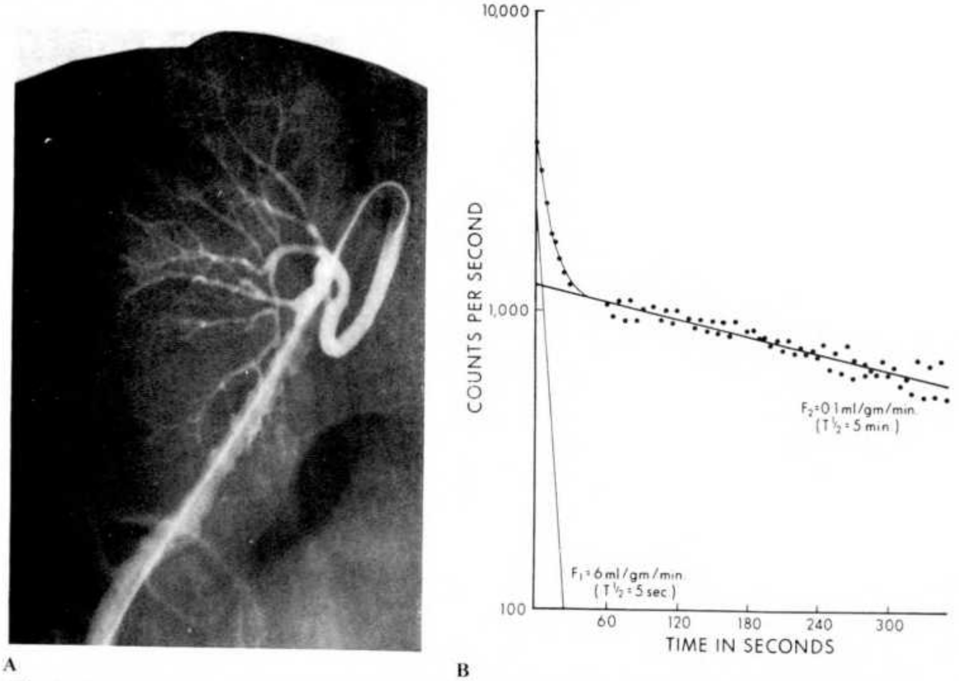

Fig. 5. Patient F. E. **A**, Arteriogram of renal transplant suspected of undergoing late rejection. **B**, Xenography of the transplant showing an essentially normal pattern. Flow for fast (F_1) and slow (F_2) components expressed in ml/g/min.

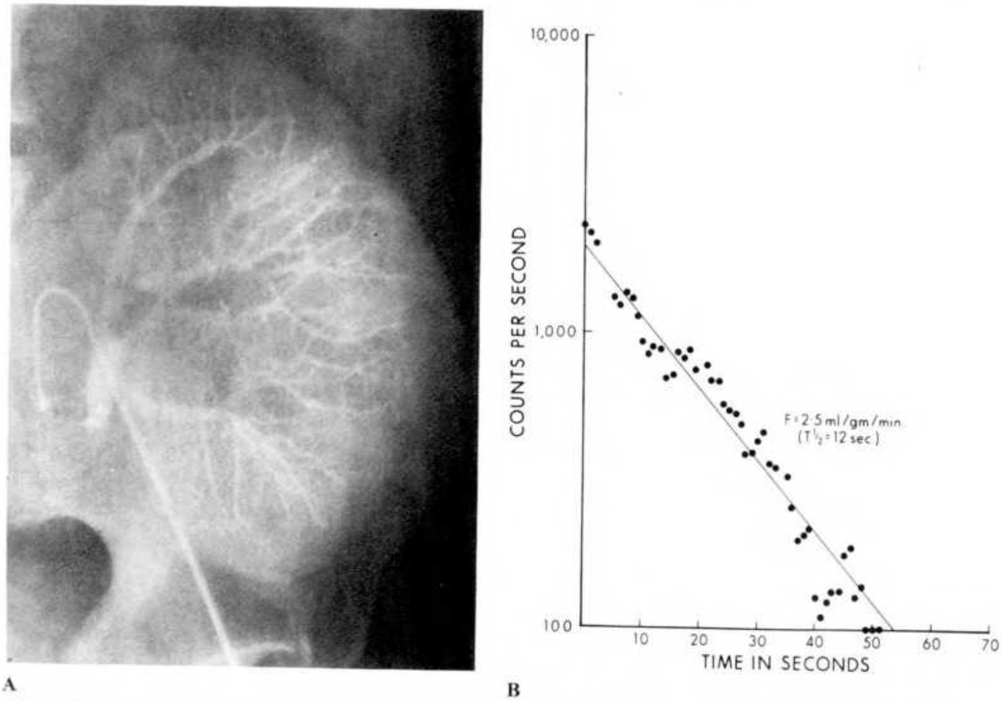

Fig. 6. Patient R. S. **A**, Arteriogram of renal transplant suspected of undergoing late rejection. **B**, Xenogram of the transplant showing that the slope is mono-exponential (and therefore abnormal for the kidney).

were in any event undergoing renal arteriography were investigated. The xenogram adds about 10 minutes to the procedure but the risk to the patient is no greater than that of selective renal arteriography alone. The radiation hazard due to the injection of 500 μCi of ^{133}Xe is negligible.

In most categories of renal pathology discussed it has been felt that the ^{133}Xe renal blood flow studies provided useful information that was of clinical value in managing the individual cases. In certain areas the method was deficient. It cannot demonstrate occlusion of a branch of the renal artery, nor can it help in distinguishing renal tumours from benign cysts.

On the other hand, in some settings it may provide more information than the arteriogram alone—such as in the quantitation of renal ischaemia, in the diagnosis of renal vein thrombosis, in the prediction of recovery of renal function following relief of obstruction and in the evaluation of possible renal transplant rejection.

The ^{133}Xe renal blood flow profile is envisaged as a study which will complement the arteriogram and thereby provide a more dynamic representation of the renal circulation. If further experience confirms our observations it is anticipated that the xenogram could become an integral part of the renal arteriogram.

Summary

The features of the ^{133}Xe renal blood flow profile in the normal kidney have been described. It is suggested that the xenogram may be particularly useful in:

1. The assessment of renal trauma cases.
2. The evaluation of the non-functioning kidney.
3. The preoperative definition of renal vein thrombosis in renal carcinoma cases.
4. The quantitation of renal ischaemia.
5. The diagnosis of transplant rejection.

The technique is recommended for the evaluation of difficult diagnosis renal problems in the hope that it may shed some light and in the knowledge that it will do no harm.

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Divided Renal Function Studies in Hypertension

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Renal artery stenosis does not always lead to hypertension; nor does the combination of renal artery stenosis and hypertension invariably imply that the hypertension is caused by a demonstrated arterial stenosis.

In spite of the development of a large number of diagnostic methods and intensive renophysiological studies during the last 20 years, it has not so far been possible to set up criteria which ensure absolutely satisfactory results of surgical treatment of renal hypertension.

Divided renal function studies have been widely used, especially by American and British investigators (Howard, Connor and Thomas, 1956; Connor *et al.*, 1960; Rapoport, 1960; Stamey, 1961). The value of such studies in the assessment of renal hypertension has been the subject of much discussion (Stewart *et al.*, 1965; Gammelgaard *et al.*, 1967; O'Conor and Simon, 1970).

Patients and Methods

In the Department of Urology K, Århus Kommunehospital, we have undertaken divided renal function studies in a group of patients with hypertension referred to us from the Departments of Internal Medicine C and Cardiology of our hospital.

These patients have been followed up in order to disclose to what extent it is possible, on the basis of these functional studies, to predict the result of surgical treatment of renal hypertension.

Table I shows the sex and age distribution of the series, which consisted of 82 patients—33 men and 49 women. As renal function studies were principally performed on patients in whom it was considered likely that surgical intervention would be beneficial, most of them were relatively young.

In all cases we used general anaesthesia with halothane, which interferes only slightly with renal function. One hour before the induction of anaesthesia, the patient was given an intravenous infusion of 1,000 ml of 5% glucose. Then polyethylene catheters were passed up the ureters, Nos. 5 to 8 being used according to the size of the ureteral orifice. The catheters were passed about 10 cm up the ureters, after which an indwelling bladder catheter, to which the ureteral catheters were fixed, was inserted. Urine was then collected from both ureters and from the bladder.

The bladder catheter was inserted in order to reveal any leakage around the ureteral catheters. Only in 8 patients, *i.e.* about 10% of the cases, did such leakage occur, and it was seen only during the last or second last 10-minute periods when the urinary output was considerable.

After the insertion of the catheters an intravenous injection of 80 mg para-aminohippuric acid (PAH) was given, followed by the infusion of a solution consisting of 1,000 ml of 5% glucose, 240 mg PAH and 40 g urea.

The position of the ureteral catheters was not checked radiographically, but the urinary flow from them was closely observed. As long as there was a rhythmic emission of urine in ample amounts and the bladder catheter did not yield any urine the collection was regarded as satisfactory.

The anaesthesia was terminated immediately after the insertion of the catheters, and urine was then collected in 4 to 6 periods each of 10 minutes.

The volumes of urine excreted were measured; quantitative determinations of the urinary levels of sodium, creatinine and PAH were made, and the serum levels of creatinine and PAH were determined repeatedly.

Complications

It has been reported that complications of divided renal function studies are both fairly frequent and relatively severe. Table II shows the complications encountered in our series. Only in 2 cases did severe complications occur. In 1, anuria developed 24 hours after the test. Ureteral catheters were inserted on both sides. After the removal of blood clots from the ureters by irrigation renal function was re-established. In the second case, a rise of blood-pressure occurred after the renal function test. The patient became drowsy, but after treatment with anti-hypertensive drugs the crisis was completely overcome.

Other complications were flank pain in a few cases, macroscopic haematuria in 14, and 2 patients suffered from dysuria for a few days after the test.

Table 1

Sex and Age Distribution of 82 Patients with Renal Hypertension subjected to Divided Renal Function Studies

Age in Years	Men	Women
<30	3	11
31-40	3	13
41-50	7	11
51-60	15	10
61-70	5	3
<70	0	1
Total	33	49

Table II

Complications of Divided Renal Function Studies in 82 Patients

	Incidence	
Complication	No.	%
Anuria	1	1
Hypertensive crisis	1	1
Flank pain	3	4
Slight fever	1	1
Haematuria	14	17
Dysuria	2	3
Total	22	27

Table III

Positive Test in a 63-year-old Man with Hypertension (230/120 mm Hg) of 2 Years' Duration, a small Right Kidney and Stenosis of the Right Renal Artery

	Left	Right
Urinary flow, ml/10 min	99	2
Urinary sodium, mEq/l	80	75
Urinary creatinine, mg %	17	69
Urinary PAH, mg %	21	74
Creatinine clearance	95	6
PAH clearance	180	9

Results

According to the results obtained the patients may be divided into 3 groups:

1. Patients with a positive test, of which an example is given in Table III. The characteristic features are a small urinary flow, a relatively low urinary sodium level, and considerable concentrations of creatinine and PAH in the urine on the affected side. The concentrations of creatinine and PAH were so pronounced that the clearances were only slightly reduced. According to Howard's and Stamey's investigations, this is the typical response in patients with hypertension caused by renal artery stenosis. The physiological explanation is thought to be that the reabsorption of water by the affected kidney is increased, with a resultant concentration of creatinine and PAH.

Of the 82 patients studied, 25 belonged to this group.

2. In this group the test was negative. The urinary flows were equal on both sides, and so were the concentrations of creatinine and PAH in the urine. An example of this is shown in Table IV.

Table IV

Negative Test in a 47-year-old Man with Hypertension (180/120 mm Hg) of 4 Years' Duration, Normal Urography and Slight Stenosis of the Right Renal Artery. Serum Creatinine 1·7 mg.

	Left	Right
Urinary flow, ml/10 min	133	146
Urinary sodium, mEq/l	20	15
Urinary creatinine, mg %	4	5
Urinary PAH, mg %	11	12
Creatinine clearance	30	41
PAH clearance	134	159

Table V

Negative Test in a 61-year-old Woman with Hypertension (140/110 mm Hg) of 7 Years' Duration, a Small Right Kidney and Stenosis of the Right Renal Artery

	Left	Right
Urinary flow, ml/10 min	51	11
Urinary sodium, mEq/l	58	47
Urinary creatinine, mg %	12	10
Urinary PAH, mg %	42	49
Creatinine clearance	47	8
PAH clearance	239	51

In the patient concerned, angiography had revealed stenosis of the renal artery on the right side, but the bilateral function test showed a negative pattern. The clearance was somewhat diminished on both sides, even more on the side where there were no signs of stenosis.

Of the 82 patients studied, 33 were in this group, including 6 (18%) with over-all impairment of renal function.

3. The third group, in which the test according to Howard's and Stamey's reports should also be regarded as negative, showed a functional pattern like that seen in group 2, without concentration of creatinine or PAH on the affected side. This is exemplified in Table V. The patient here had stenosis of the artery of the right kidney, which was very small. On the right side, the urinary flow was markedly reduced, and so were the creatinine and PAH clearances.

This pattern was observed in 24 patients, including 10 (40%) with distinct over-all renal impairment.

Evaluation of the Results

The value of divided renal function studies can be assessed only in the 25 patients who were afterwards subjected to arterial reconstruction (11 cases) or unilateral nephrectomy (14 cases).

The indication for surgery was based on the clinical state of the patient, the degree of hypertension, the I.V.P. and the arteriographic findings. The divided renal function studies were carried

Table VI

Survey of the Results of Operation in 15 Patients with Positive Tests

	Patient No.	Lesion	Urinary Flow ml/10 min		Urinary Creatinine mg %		PAH mg %		Creatinine Clearance	
			Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.
A	33	Stenosis of left renal artery	0	18	...	39	...	34	...	47
	36	Stenosis of right renal artery	83	7	18	128	...	...	...	...
	38	Stenosis of right renal artery	201	0	6	...	127	...	114	...
	69	Stenosis of right renal artery	61	18	11	22	25	57	58	32
	72	Slender right renal artery Pheochromocytoma	97	4	10	13	37	46	72	8
	77	Occlusion of right renal artery and aorta	24	1	7	120	18	58	12	8
	82	Stenosis of left renal artery	12	129	12	6	41	20	12	61
	85	Stenosis of right renal artery	20	11	13	34	33	71	22	32
B	1	Stenosis of right renal artery	170	11	6	96	9	99	82	42
	84	Stenosis of left renal artery	8	37	89	32	103	35	49	84
	86	Stenosis of right renal artery	99	2	17	69	21	74	95	6
C	15	Slender right renal artery	225	3	4	10	13	...	66	...
	32	Stenosis of right renal artery	73	1	11	...	...	...	62	...
	74	Stenosis of right renal artery Stenosis of left renal artery	193	21	3	7	10	24	59	14
	83	Stenosis of right renal artery	236	113	2	3	8	12	57	47

Groups A, B, C—see text

Table VII

Survey of the Results of Operation in 10 Patients with Negative Tests

	Patient No.	Lesion	Urinary Flow ml/10 min		Urinary Creatinine mg %		PAH Clearance		Creatinine Clearance	
			Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.
D	2	Stenosis of right renal artery	64	32	20	13	30	15	66	18
	61	Stenosis of right renal artery	51	11	13	10	42	49	47	8
	67	Right hydronephrosis	38	13	26	32	67	49	82	36
	76	Stenosis of left renal artery	27	24	10	4	44	17	35	13
E	68	Left hydronephrosis Slender left renal artery	2	75	8	19	8	41	1	77
F	30	Stenosis of both renal arteries	27	33	19	11	31	17	43	20
	56	Stenosis of left renal artery	12	15	44	44	95	98	46	55
	58	Tumour of right kidney Stenosis of left renal artery	52	65	10	12	29	33	36	55
	62	Stenosis of right renal artery	167	25	5	5	12	11	64	9
	64	Tumour of right kidney	120	66	5	5	...	...	36	19

Groups D, E, F—see text

PAH Clearance			Observation Period in Years	Blood-pressure Level	
Lt.	Rt.	Operation		Preop.	Postop.
...	64	Left nephrectomy	4	210/110	160/100
...	...	Transplantation of right renal artery	2	180/110	145/100
266	...	Right nephrectomy	2	220/120	130/80
143	79	By-pass operation of right renal artery Later right nephrectomy	2	180/110	130/80
242	19	Right nephrectomy + adrenalectomy	2	200/120	140/80
36	6	Right nephrectomy + transplantation of the aorta	3	230/150	170/100
32	186	Left splenorenal anastomosis	½	220/115	140/90
62	86	Transplantation of right renal artery	2	180/120	150/90
252	166	Thrombendarterectomy of right renal artery	2	235/125	170/110
159	256	Plastic operation of left renal artery (vein patch)	2	210/130	180/110
180	9	Right nephrectomy	2½	230/120	180/110
177	...	Left nephrectomy	3	215/115	210/110
...	...	Right nephrectomy	3	210/105	210/110
188	46	Right nephrectomy	4	200/100	180/100
290	235	Transplantation of right renal artery	½	240/150	200/120

PAH Clearance			Observation Period in Years	Blood-pressure Level	
Lt.	Rt.	Operation		Preop.	Postop.
153	37	Right nephrectomy	5	225/130	150/80
239	51	Right nephrectomy	4	240/110	140/80
270	75	Right nephrectomy	4	210/110	140/90
116	42	Left splenorenal anastomosis	2	230/110	150/100
1	253	Left nephrectomy	3	230/140	160/110
139	90	Plastic operation of both renal arteries	0	230/130	Died in relation to operation
104	123	Left splenorenal anastomosis	4	230/125	230/130
123	178	Right nephrectomy	½	210/120	210/110
274	52	Plastic operation of right renal artery	5	215/105	200/120 (occlusion of renal artery)
...	...	Right nephrectomy	1	220/120	200/120

out along with the other examinations for the purpose of a later evaluation of the test and were not used for selection of the candidates for surgery.

A brief account of the results of operation obtained in patients with (1) positive and (2) negative tests, respectively, is given below.

Table VI shows the results of operation in patients with positive renal function tests divided into 3 groups. The first group (A) comprises 8 patients in whom a definite improvement in the blood-pressure status occurred postoperatively. The second group (B) consisting of 3 patients showed some postoperative improvement, while the last 4 patients (C) did not benefit from the operation.

Thus, an improvement in the blood-pressure status was obtained in 10 out of 15 patients with positive tests, *i.e.*, 73%.

Table VII is a survey of the results of operation in the 10 patients with negative tests, also divided into 3 groups. The first group (D) comprises 4 patients who showed a definite improvement in hypertension; the second group (E) consists of only 1 patient who did derive some benefit from the operation; in the third group (F) of 5 patients surgical treatment did not reduce the blood-pressure level. This third group includes 1 patient who died in the early postoperative period; she was a 42-year-old woman with fibromuscular hyperplasia of both renal arteries.

Improvement in the blood-pressure status was thus obtained in 5 out of 10 patients with negative tests, *i.e.*, 50%.

Discussion

The results show that divided renal function studies—at least with the technique employed in this study—do not provide an unequivocal answer to the question whether the hypertension is caused by renovascular changes.

In the patients with positive tests, surgical treatment led to improvement in 73% of the cases. However, improvement was also obtained in patients with negative tests, although with a slightly lower frequency, *viz.* 50%. A statistical comparison of the results in the 2 groups did not reveal any significant difference.

The causal relation between hypertension and renovascular changes is presumably so complex that it cannot be disclosed by divided renal function studies. The condition of the "unaffected" kidney must obviously play an important role. It might therefore be suspected that the results of surgical treatment (nephrectomy or arterial reconstruction) would be poorer if the over-all renal function was reduced—indicating functional impairment also of the "unaffected" kidney. However, an analysis of the 25 patients who underwent operation with special reference to this problem did not confirm such a suspicion. The results obtained were just as good in the cases where the "unaffected" kidney showed impaired function as in those where the clearance was perfectly normal.

It is therefore not reasonable to use divided renal function studies as a screening procedure since the risks involved in renography and excretory urography are far less.

However, the test must be recommended in cases in which nephrectomy is contemplated. Creatinine clearance levels in the present series revealed impaired function of the "unaffected" kidney in many cases—a fact which, although it does not definitively contra-indicate nephrectomy, should presumably lead to further reluctance in its use.

Conclusions

Divided renal function studies in patients with renal hypertension have been widely used in the selection of patients for surgical treatment. However, the results obtained in this study did not provide a definite answer to the question whether improvement in hypertension can be obtained by surgical intervention.

Divided renal function studies are associated with a relatively high frequency of complications. Although most of these complications are not severe, the procedure cannot be recommended as a screening test.

On the other hand, its use must be advised in cases of renal hypertension in which nephrectomy is contemplated, as it may reveal incipient functional impairment of the "unaffected" kidney.

Summary

Divided renal function studies were performed in 82 patients with hypertension and renal artery stenosis.

The results were divided into 3 groups: (1) Positive tests with reduced urinary flow and increased creatinine and PAH concentrations in the urine on the affected side. (2) Negative tests with urinary flow and creatinine and PAH concentrations in the urine equal on both sides. (3) Negative tests with markedly reduced urinary flow on one side, but with equal creatinine and PAH concentrations on both sides.

Of the 82 patients, 25 were subjected to nephrectomy or arterial reconstruction. In the latter, the test had been positive in 15 and negative in 10. Postoperative improvement in the hypertension was almost equally frequent in the 2 groups.

The analyses of the urine samples were performed in the Department of Clinical Chemistry, Århus Kommunehospital.

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Neonatal Renal Tumours

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It has long been recognised that renal tumours discovered in the first year of life carry a better prognosis and therefore perhaps differ from those diagnosed in older children. Jacobi (1886) and Paul (1886) described renal masses in foetuses and neonates, the nature of which has since been in debate. Kay and others (1966) regarded them as hamartomata, whereas Bolande and others (1967) considered them to be a well differentiated variety of nephroblastoma. Favara and his colleagues (1968), although confident the changes were not those of typical Wilms' tumour, could not decide whether they represented benign leiomyomata or hamartomata. The vigorous treatment by radiotherapy and chemotherapy, currently associated with surgery in the management of nephroblastoma carries an appreciable morbidity. It would seem desirable that these cases of renal abnormalities in infancy should be treated along more conservative lines than growths

Table

Case	Age at Presentation	Sex	Birth Weight kg	Kidney Affected	Intravenous Pyelogram	Blood Urea in mg%	Therapy	Therapy	Mitotic Rate of Tumour as Mitoses/100 High Power Fields
1	1 Day	F	3·2	Right	Right-sided renal tumour	15	Right nephrectomy actinomycin D	Died at 18 days	3
2	1 Day	F	3·46	Right	Right kidney displaced downwards by tumour	57	Right nephrectomy	Alive and well after 2 years	13
3	3 Days	M	2·55	Right	Right renal enlargement with displacement of upper calyces	35	Right nephrectomy	Alive and well after 3½ years	2
4	6 Days	M	1·64	Right	Lateral and downward displacement of right kidney	24	Right nephrectomy	Alive and well after 7 years	35
5	7 Days	M	3·15	Right	Right renal enlargement with loss of calyceal outline of lower ⅓	34	Right nephrectomy	Alive and well after 7½ years	13
6	7 Days	F	2·50	Right	Right-sided displacement and distortion of upper calyces	20	Right nephrectomy	Alive and well after 5 years	19
7	3 Days	M	4·25	Right	Lateral displacement of right renal pelvis	18	Right nephrectomy	Died at 9 days peritonitis	32

occurring in older patients, provided such treatment can be shown to be effective (Kay *et al.*, 1966; Bolande *et al.*, 1967).

This paper describes 7 cases of renal growths in neonates, considers their nature and discusses their management.

Cases

The clinical details, management and outcome of the 7 patients are summarised in the table. All presented with a right sided abdominal mass found on routine examination and all, with the exception of Case 1, whose development has been associated with hydramnios, were the products of normal pregnancy.

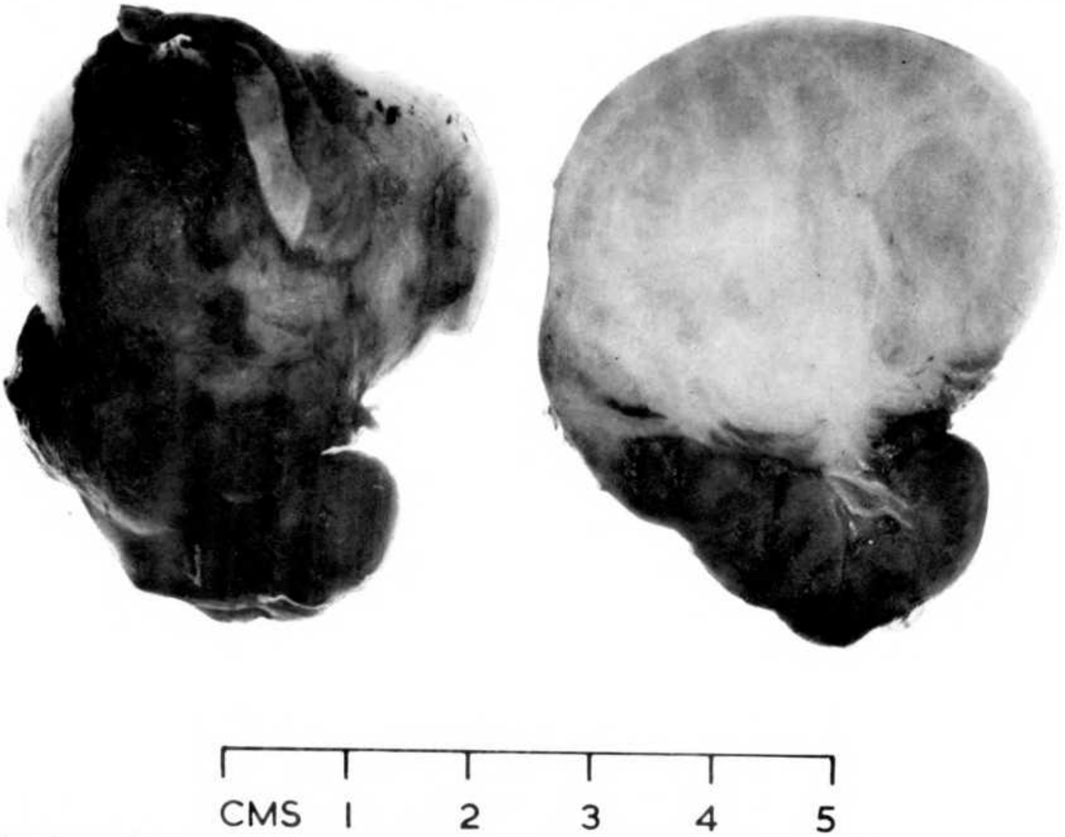

Fig. 1. Case 3. Tumour is clearly seen through the renal capsule; whorled pattern on cut surface.

All were treated by nephrectomy and Case 1 died of uraemia attributed to actinomycin D therapy. Case 7 died of postoperative complications. Postmortem showed no extension of the disease beyond the kidney in either case. The remaining 5 children are alive and well at periods ranging from 2 to 7½ years.

Pathological Findings

All kidneys examined were grossly and histologically similar. The renal outline was distorted by a mass, of which the largest diameter was 5 cm and whose surface was covered by renal capsule

(Fig. 1). Multiple blocks from each tumour were stained with haematoxylin and eosin, Masson's trichrome, Van Gieson's mixture, phototungstic acid haematoxylin and Gordon and Sweet's reticulin stains.

The tumour is composed of interlacing bands of closely packed elongated cells with eosinophilic cytoplasm. The nuclei are elongated with rounded ends, vesicular and monomorphic. Collagenous and smooth muscle elements are present throughout the tumour. Foci of mature glomeruli and tubules are scattered through the tumour (Fig. 2). Nodules of cartilage are seen in some tumours and all show dilated tubules beneath the renal capsule. There is no invasion of capsule, ureter, renal vessels or lymphatics by tumour. The junction with the kidney is irregular as bands of kidney and tumour interdigitate and merge imperceptibly with no intervening capsule (Fig. 3). Tubular dilatation is seen in the uninvolved portion of the kidney.

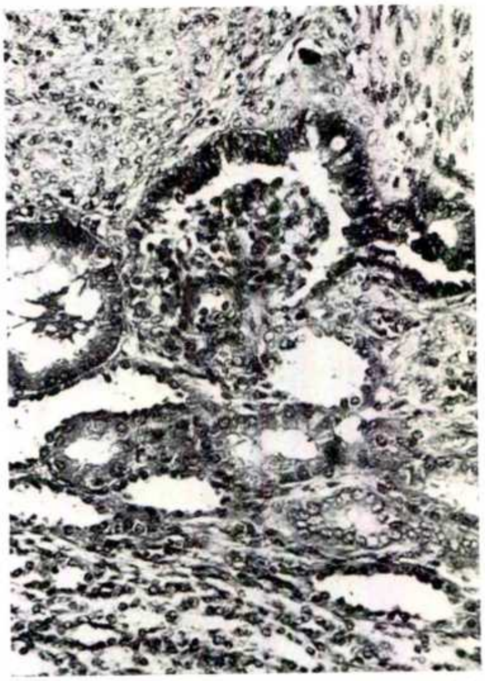

Fig. 2. Case 6. Immature glomerulus and tubules within the tumour. Haematoxylin and eosin. × 100.

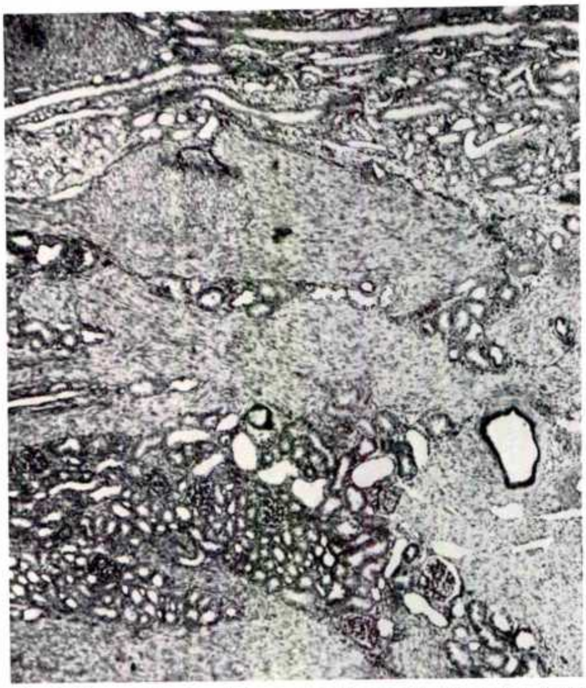

Fig. 3. Case 5. Bands of tumour cells extend between normal nephrons. A few tubules are dilated. Haematoxylin and eosin. × 10.

Large variations of mitotic activity were observed between the growths.

Comment

Renal neoplasms in children are currently treated by a combination of surgery, radiotherapy and chemotherapy. Radiotherapy in childhood may result in growth impairment (Dawson 1968) and chemotherapeutic agents appear to be particularly toxic in the neonatal period (Kay *et al.*, 1966; Wigger, 1969). It is most desirable that these methods of treatment should not be used unnecessarily.

Nephroblastoma is uncommon under the age of 1 year (Klapproth, 1959; Hilton and Keeling, 1970). Renal growths seen in stillbirths and neonates are unlike those found in older children; those cases with adequate histological descriptions stress the appearance of intertwining bundles of spindle cells with scattered groups of tubules between the bundles (Jacobi, 1886; Paul, 1886; Semb, 1894; Kastner, 1921). Paul (1886) remarked that the groups of tubules were immature, not neoplastic and Kastner (1921) described islands of normal tubules and glomeruli lying within the tumour. Adjacent groups of tubules may be lined by a single layer of cuboidal or columnar cells, unlike those of nephroblastoma which are lined by several layers of tall hyperchromatic cells. In nephroblastoma, mesenchymal tissues may predominate, but uniformity of structure is most uncommon. The loose, basophilic embryonic mesenchyme which is almost invariably present is absent in the neonatal tumour. A capsule is usually apparent in nephroblastoma but the limits of neonatal tumours are indefinite and blend imperceptibly with surrounding kidney (Zuckerman *et al.*, 1947). Kay *et al.* (1966) describe the transition between kidney and tumour as gradual and irregular.

General agreement has not been reached regarding the nature of those changes found in infancy. Wigger (1969) describes 5 cases in neonates and separates them from nephroblastoma, as do Richmond and Dougall (1970) and Waisman and Cooper (1970) by their clinical course and histological features. Wright (1970) however, describes a well differentiated Wilms' tumour in a neonate and Beckwith (1970) who has seen frank Wilms' tumours showing identical histology to that described in neonates, regards this as evidence that these are nephroblastoma.

Our cases, which presented a characteristic histological appearance, were treated by surgery alone, after the death of Case 1 which was attributed to actinomycin D. Their favourable subsequent progress suggests that they were not typical nephroblastomata, which, it is well known, generally fare badly unless surgery is associated with radiotherapy and chemotherapy. We believe that a group of cases occurring in the neonatal period are hamartomatous rather than malignant and can be distinguished histologically from nephroblastomata.

The separation of this group of tumours is not merely of academic interest, but also of practical importance as they should be managed by surgery alone; added treatment by irradiation and chemotherapy is irrelevant and potentially destructive.

Summary

Seven cases of neonatal renal tumours are described and their histological differences to those of nephroblastoma are discussed.

From these and their favourable prognosis, they are considered hamartomatous and emphasis is laid on their management by surgery alone.

We would like to thank Professor A. E. Claireaux and Mr D. Innes Williams for their helpful criticism of this paper and the Photographic Department of the Hospital for Sick Children for Figure 1.

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Sodium Excretion after Relief of Urinary Tract Obstruction in Children

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The disturbance of renal physiology consequent upon urinary tract obstruction is incompletely understood. Furthermore, the results of relief of urinary tract obstruction appear capricious, for on some occasions a substantial rapid improvement in glomerular filtration rate occurs, but in others there is no improvement in renal function.

It is well-established that the usual renal response to surgical stress is a reduced excretion of salt and water (Le Quesne, 1957; Wilkinson, 1969). These principles are the basis of recommendations for restricted intakes of salt and water during the postoperative period. Sometimes, however, after relief of urinary tract obstruction there is a substantial increase in urinary sodium excretion (Bricker *et al.*, 1957) which may result in extracellular fluid volume depletion unless losses are replaced. The occurrence of such postobstructive natriuresis is unpredictable, and its significance in terms of renal function is uncertain.

In a previous study of renal function in children with urinary tract obstruction (Barratt and Chantler, 1970) it was found that after relief of obstruction, glomerular filtration rate (GFR) increased most in those children in whom, before operation, the ability to dilute the urine in response to water loading was restricted. This finding was interpreted as indicating reabsorption of an increased proportion of the filtered sodium and water by the proximal tubule in patients with a partially reversible depression of GFR, and it was postulated that there was reduced GFR per nephron with increased fractional proximal reabsorption of filtrate attributable to hydrodynamic factors. Similar conclusions have been drawn from animal experiments (Suki *et al.*, 1966). It seems possible, therefore, that successful relief of the urinary obstruction results in more filtrate reaching a tubular system in which back pressure no longer favours the reabsorption of sodium and water. We have examined this hypothesis in children with obstructive nephropathy by measuring GFR and urinary sodium excretion before and after relief of urinary obstruction.

Patients and Methods

50 children with urinary tract obstruction aged from 2 months to 11 years were studied. The diagnosis of urinary tract obstruction was based on clinical grounds and radiological evidence of dilatation of the urinary system. Some children had congenital and others acquired obstructive lesions; in some the obstruction was unilateral and in others bilateral. As a general principle, the guide-lines of Wilkinson (1969) were followed in the administration of salt and water during the postoperative period, but a systematic policy of intravenous fluid therapy was not observed, and intravenous infusion was discontinued in nearly all within 48 hours of operation.

The urine sodium concentration (U_{Na}) was estimated by emission spectrophotometry on 24-hour urine specimens collected on the day before operation and on the first 3 postoperative days.

Results have been expressed per kg body weight. The increment in urine sodium excretion rate ($\Delta U_{Na}V$) has been calculated as a percentage of the preoperative level:

$$\Delta U_{Na}V = \frac{\text{Postop } U_{Na}V - \text{Preop } U_{Na}V}{\text{Preop } U_{Na}V} \times 100.$$

In 18 of these patients, in whom the obstruction was infravesical, bilateral or affecting a solitary functioning kidney (Table I), the GFR was measured before and 1 week after successful relief of urinary tract obstruction. Only 5 of these patients received intravenous infusions, which were discontinued within 36 hours of operation in all cases.

Table I

Preoperative and postoperative urinary sodium excretion and GFR in children with obstructive nephropathy.

			Preoperative		Postoperative			
Patient	Age (years)	Obstructive Lesion	GFR (ml/min/ 1·73 m² SA)	$U_{Na}V$ (mEq/kg/ 24 h)	GFR (ml/min/ 1·73 m² SA)	$U_{Na}V$ Day 1 (mEq/kg/ 24 h)	$\Delta U_{Na}V$ %	ΔGFR %
T. J.	2	Ureterocele	89·9	3·0	75·3	0·9	−70	−16
M. R.	5	Urethral valves	131·9	2·4	117·4	1·9	−21	−11
N. D.	6	Neurogenic bladder	32·9	2·7	31·1	2·2	−19	−5
M. S.	2/52	Dysplastic urinary tract with obstructed ureters	21·7	0·8	21·6	1·2	+50	+0
P. J.	5	Urethral valves	75·9	3·9	80·2	4·3	+10	+6
R. I.	3/12	Urethral valves	83·0	2·8	90·0	3·7	+32	+8
S. B.	3/12	Bilateral pelvi-ureteric junction obstruction	81·1	1·1	89·0	2·9	+164	+10
S. O.	6	Solitary obstructed pelvic kidney	7·9	0·5	8·8	0·4	−20	+10
C. I.	8	Bilateral primary mega-ureter	120·3	3·0	132·9	3·3	+10	+10
J. D.	5	Neurogenic bladder	17·6	3·2	19·8	5·9	+84	+13
K. S.	10	Bilateral single ectopic ureters	73·1	1·7	85·1	0·9	−45	+16
A. R.	10	Bilateral primary mega-ureter	44·5	4·0	54·1	5·6	+40	+22
J. H.	8	Bilateral primary mega-ureter	67·5	0·4	83·1	0·8	−100	+23
J. R.	3/12	Urethral valves	62·8	0·8	78·3	2·1	+163	+25
D. M.	4	Urethral valves	108·7	2·4	140·2	3·2	+33	+29
S. O.	6	Bilateral primary mega-ureter	36·9	2·6	48·3	1·4	−46	+31
A. W.	2	Horse-shoe kidney with bilateral pelvi-ureteric junction obstruction	38·9	1·5	65·0	3·6	+40	+67
T. G.	11	Solitary obstructed kidney	28·4	1·9	53·2	4·4	+132	+87

GFR was estimated from the plasma clearance or ^{51}Cr-EDTA (Chantler and Barratt, 1972), corrected to 1·73 m² surface area (SA) using the formula of Dubois and Dubois (1916), and the increment (ΔGFR) calculated:

$$\Delta GFR = \frac{\text{Postop GFR} - \text{Preop GFR}}{\text{Preop GFR}} \times 100.$$

The coefficient of variation of replicate estimates of GFR in the same individual by this technique is 3·5%, and therefore values for ΔGFR in excess of 11% represent a significant change.

Results

Preoperative urinary sodium excretion was 1·90±0·98 mEq/kg body weight/24 hours, and on the first 3 postoperative days was 2·64±1·47, 1·99±1·07 and 1·64±1·09 mEq/kg body weight/24 hours (mean±SD) (Table II).

The changes in mean urine sodium excretion from preoperative levels were not significant, although the sodium excretion on the first postoperative day exceeded the preoperative level in 39 of the 50 cases and $\Delta U_{Na}V$ was 59±11% (SEM, $n = 50$); on the second postoperative day it was 48±26% (SEM, $n = 50$) and on the third postoperative day 27±26% (SEM, $n = 46$).

Table II

Urine sodium excretion and the percentage increase ($\Delta U_{Na}V$) after relief of obstructive nephropathy. $\Delta U_{Na}V$ on day 1 is significantly greater than zero.

	Urinary Sodium Excretion (mEq/kg/24 h) mean±SD	$\Delta U_{Na}V$ % mean±SEM
Preoperative	1·90±0·98	...
Postoperative, Day 1	2·64±1·47	59±11
Postoperative, Day 2	1·99±1·07	48±26
Postoperative, Day 3	1·64±1·09	27±26

$\Delta U_{Na}V$ on the first postoperative day was significantly ($P<0{\cdot}05$) greater than zero, but the differences on the second and third days were not significant.

The urinary sodium excretion before operation and on the first postoperative day, and the GFR before and 1 week after surgery in the 18 selected cases are given in Table I.

All of the 12 patients in whom the urinary sodium excretion was greater on the first postoperative day than preoperatively were found to have an increase of GFR at 1 week, in contrast to only 3 of the 6 patients in whom postoperative urine sodium was less than the preoperative level ($P<0{\cdot}05$; exact test (Finney *et al.*, 1963) (Fig. 1). There was a significant positive correlation between ΔGFR and $\Delta U_{Na}V$ (Spearman rank-correlation coefficient = 0·45;$0{\cdot}05>P>0{\cdot}01$; Hayslett, 1971).

Discussion

The data indicate that the urine sodium excretion on the first postoperative day frequently exceeds preoperative levels in children undergoing relief of urinary tract obstruction. There is a correlation between the increment in sodium excretion on the first postoperative day and the increase in GFR at the end of the first postoperative week. The observations reported are compatible with the hypothesis that rapidly reversible impairment of renal function is characterised by enhanced proximal reabsorption of sodium and water with a tendency to natriuresis when the obstruction is relieved. Such a functional disturbance would also account for the characteristic density of the obstructive pattern of the nephrogram, which is determined in part by the extent of proximal tubular reabsorption of sodium and water (Sherwood, 1971).

An alternative explanation of the data, however, is that those patients who have received more saline during the postoperative period, and hence excreted more sodium in the urine, have as a consequence an improved GFR at 1 week. The data are not available to refute this possibility, but as only 5 of the patients had intravenous infusions, and they for less than 36 hours, the explanation seems improbable.

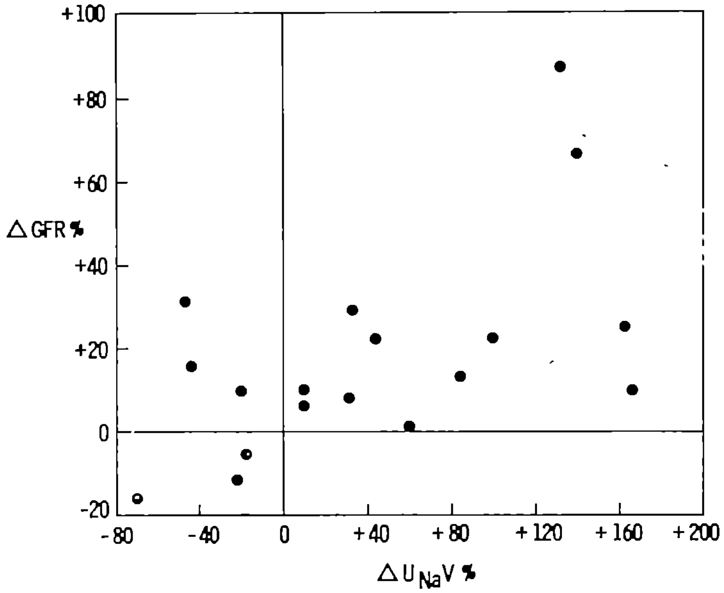

Fig. 1. The correlation between increments in urinary sodium excretion ($\Delta U_{Na}V$) and glomerular filtration rate (ΔGFR) is significant (Spearman rank-correlation coefficient = 0·45; 0·05 > P > 0·01).

Conclusion

Whichever explanation of the observed results is correct, the therapeutic implications are clear, namely that the sodium intake of children undergoing relief of obstructive nephropathy should not be restricted in the postoperative period, and as the mean urine sodium excretion on the first postoperative day was 2·6 mEq/kg, it would seem appropriate to match this by a similar intake.

Summary

After relief of obstructive nephropathy urinary sodium excretion rose in 39 of 50 children to a mean in the whole group of 59% above preoperative levels.

There was a significant positive correlation between the increase in sodium excretion in the first 24 hours after operation and the increase in GFR at 1 week.

The data are compatible with the hypothesis that the reversibly obstructed kidney is characterised by nephron underperfusion and enhanced proximal reabsorption of filtrate due to hydrodynamic factors.

The sodium intake should not be restricted during the postoperative period in children after obstruction of the urinary tract has been relieved.

We thank Professor J. F. Soothill, Mr D. Innes Williams and Professor A. W. Wilkinson for advice. One of us (S. G.) was supported by a grant from the Joint Research Board of the Hospital for Sick Children and the Institute of Child Health, and subsequently from the Wellcome Research Foundation during the study.

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Pyelo-Colonic Diversion in Children

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The late results of uretero-ileo-cutaneous diversion in children fall well short of perfection in terms of preservation of upper tract and kidney structure and function, and the later the results the less perfect they are. The evidence that this was general experience was, until recently, based more on personal discussions than on perusals of the literature. However, Roy and De Domenico (1972), Scott (1973) and Schmidt *et al.* (1973) have now reported that postoperative upper tract dilatation has occurred in, respectively, 32 %, 40 % and 28 % of their patients who previously had a normal upper tract. Scott (1973) has drawn attention to the important fact that the onset of deterioration is generally delayed until at least 2 years after operation and may be as late as 7 years. When the upper tract is already dilated, uretero-ileostomy is technically easier and the operation can lead to early improvement, but in the long term urinary stasis and infection commonly persist and calculus formation is a frequent complication (Bowles and Tall, 1967; Malek, Burke and DeWeerd, 1971; Dretler, 1973).

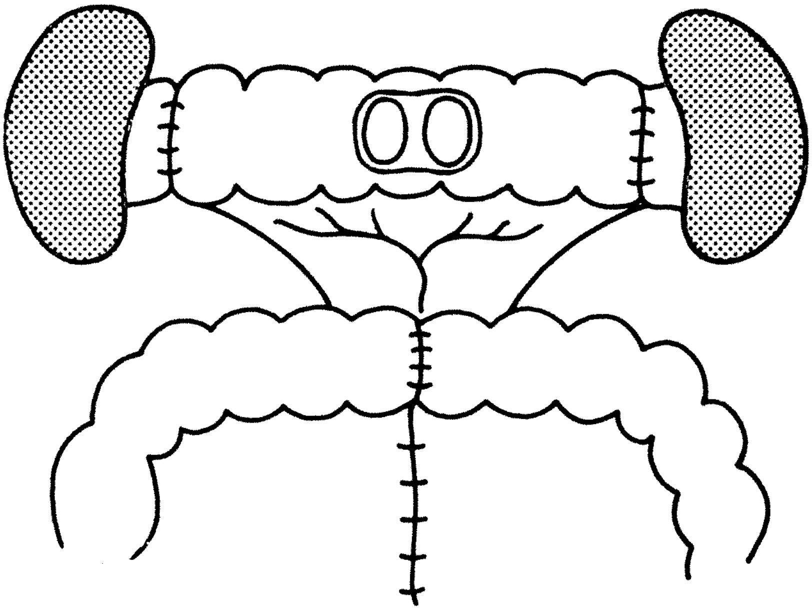

Fig. 1. Diagram of anatomy of pyelo-colonic diversion.

Postoperative deterioration of a normal upper tract and persistent stasis in an already dilated upper tract may result from such identifiable causes as stomal stenosis, the use of an excessively long and redundant conduit or uretero-ileal strictures. Often, however, no such lesions are evident. Scott (1973) found that occlusion of an ileal stoma can lead to very high pressures within the conduit and he suggests that intermittent or partial obstruction by clothing or appliances may be significant. However, fluoroscopic observation of a contrast-containing ileal conduit shows, especially when it is of some years standing, that the bowel peristalsis has limited propulsive power and the contractions have mainly a churning effect. The unsatisfactory late results of uretero-ileostomy may therefore simply be due to the inherent limitations of the procedure; ileum was not designed to transport urine and in the long term it may prove inadequate to the task so that kidney emptying becomes impaired. This is particularly likely to occur when the conduit is long and when the ureters are chronically dilated and of poor contractibility.

In an attempt to overcome the late disadvantages of uretero-ileostomy and to improve kidney drainage the author has performed pyelo-colostomy in children requiring external diversion in the presence of moderate to severe upper tract dilatation (Fig. 1). Markland (1969) has reported a similar procedure but he performed the operation only in patients with massive hydronephroses and advanced renal failure.

Technique

Bowel preparation, employing oral neomycin and neomycin colonic washouts, is carried out for 4-5 days before surgery.

The abdomen is opened through a transverse incision crossing the midline about 2 inches below the umbilicus and curving upwards towards the flank on each side. The hepatic and splenic flexures of the colon are mobilised and the kidneys exposed. The pelvis of each kidney is divided, care being taken that the proximal end has an adequate blood supply. The ureter is resected as far as can be conveniently reached. An appropriate length of transverse colon, supplied by the middle colic vessels, is isolated and intestinal continuity is restored by anastomosing the colonic flexures. The transverse colon is irrigated free of faecal matter, using a solution of neomycin. Each extremity of the conduit is anastomosed to the appropriate renal pelvis. On each side a Jacques catheter, with extra holes cut, is passed through the kidney parenchyma to splint the pyelo-colonic anastomosis and to provide external drainage after operation; the catheter is brought out through a stab incision in the flank. The umbilical scar is excised, preserving a V-shaped skin strip and the middle of the transverse colon is brought through the aperture to the abdominal surface. The skin strip is passed through the mesocolon in order to maintain a colostomy spur. After closure of the abdominal incision the colon is opened and the edges of the bowel are everted and sutured to the skin edges. The nephrostomy catheters are removed after 6 or 7 days.

Results

Eight children, 7 girls and 1 boy, between the ages of 1½ and 11 years who have had pyelo-colostomy performed have been followed for periods of between 1 and 2½ years. The indications for diversion were neurogenic bladder due to spina bifida or sacral agenesis in 6 and vesical exstrophy in 2. In 1 of the spina bifida cases bilateral ureterostomies had been performed previously. In the exstrophy cases bladder reconstruction had failed to produce urinary control and had led to pyelo-ureteral dilatation with, in 1 child, calculus formation. In all cases the upper urinary tract was dilated prior to operation and in 4 children there was significant parenchymal damage either unilaterally or bilaterally.

Follow-up intravenous urography has shown that in 7 cases pyelo-calyceal dilatation has improved (Fig. 2) or remained unaltered. One girl developed strictures at both pyelo-colonic anastomoses; routine intravenous urography 10 months after operation showed increased dilatation of both kidneys. The strictures were demonstrated by "loopograms" and it was possible to inspect the stenoses through a sigmoidoscope passed into the conduits; attempted dilatation by bougies was unsuccessful. Reanastomosis was carried out bilaterally through separate flank incisions. Stomal stenosis has not occurred in any patient although in 1 slight stomal retraction has occurred. In 5 children the required length of the conduit was overestimated at surgery and some degree of colonic prolapse later developed at the stoma; in 3 this was of sufficient severity to require trimming of the redundant bowel. No case has shown any serum electrolyte disturbances. Catheterisation of the conduits has demonstrated minimal quantities of residual urine, of the order of 5 ml; there has been no significant difference between the amounts obtained from the right and the left conduits. Bacteriological examinations of the catheter specimens have given varying results and in view of the difficulties of excluding contamination of the catheter at the stoma, no definite conclusions have been reached on this point. The central abdominal stoma has proved very satisfactory for the fitting of a collecting appliance (Fig. 3). All patients are clinically well and parents noted obvious improvement in the child's general health since the diversion.

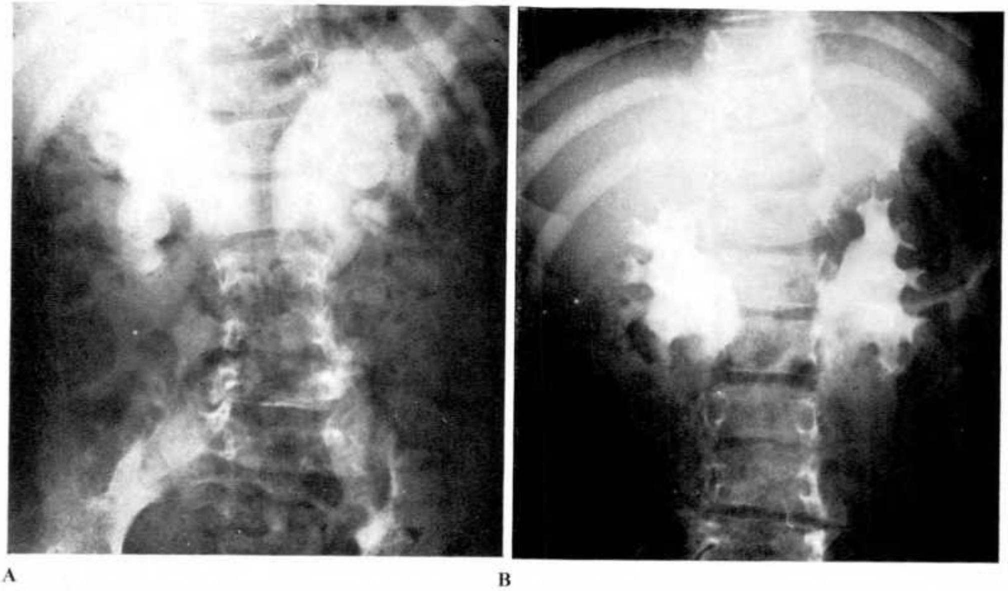

Fig. 2. Intravenous urograms in 11-year-old boy with spina bifida. **A,** Before diversion. Marked upper tract dilatation. **B,** 10 months after pyelo-colostomy. Normal calyceal pattern.

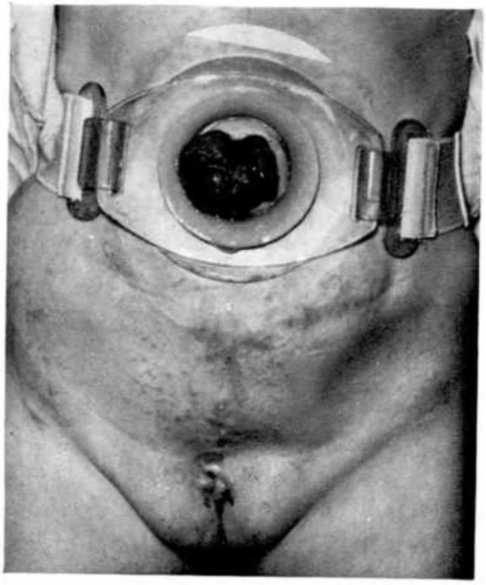

Fig. 3. Pyelo-colostomy stomata, somewhat prolapsed, at site of umbilicus in a 5-year-old girl who had bladder exstrophy.

Discussion

There are several methods of providing external drainage of a dilated upper urinary tract which may avoid the unfavourable late results of the uretero-intestinal conduit. King and Scott (1964) employed a pyelo-ileal conduit but this technique has the disadvantage of needing a very long ileal segment. Cutaneous ureterostomies, either as twin stomata or as trans-uretero-ureterostomy with a single stoma require that at least one ureter is markedly dilated, in order to avoid stomal stenosis, and sufficiently lengthened to come to the surface freely; such features are not likely to be associated with effective ureteric peristalsis.

With pyelo-colostomy, imperfectly draining ureters are eliminated and each kidney pelvis is drained directly by a portion of transverse colon. The ability of the colon to transport urine is not likely in the long run to be any better than that of the ileum but each conduit is quite short; in a 5-year-old child it is about 5-6 inches long. The left conduit is acting in an antiperistaltic direction but Mogg (1968) has shown that this is not relevant in the case of the colon and postoperative studies in my cases have demonstrated no significant difference between the quantities of residual urine in the two conduits. The operation is not free of the risk of anastomotic stricture, which occurred bilaterally in 1 case, but the complication should be avoidable by ensuring a wide anastomosis and adequate vascularity of the renal pelves and the extremities of the colon. Pyelo-colostomy offers the unique advantage that the anastomoses and the pelves are accessible to endoscopic observation.

Clearly the virtues or otherwise of any urinary diversion cannot be adequately assessed until a follow-up of some 10 years is available but, with the exception of the child who developed anastotomotic strictures, the early results of pyelo-colostomy have proved satisfactory in this series and the method may avoid the late disadvantages of orthodox conduit diversions when the upper tract is dilated and the ureters thus possess poor contractility and propulsive power.

Summary

External urinary diversion by the method of pyelo-colostomy has been performed in 8 children.

It is suggested that this procedure may give better long-term results than cutaneous uretero-ileostomy when the ureters are dilated and of poor contractility.

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The Management of Kidney Transplants Damaged during their Removal from the Donor

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The removal of kidneys from a cadaver donor is not an easy procedure. The operation may be hampered by poor light, insufficient assistance and the presence of blood in the retroperitoneal tissues. To minimise the amount of ischaemic damage to the kidneys, the surgeon will try to hurry and a combination of these factors may result in the kidney being damaged during removal.

A few years ago it was usual for the donor's kidneys to be used in the centre that removed them. If the surgeon knowingly damaged a kidney he could discard it without further ado. Nowadays, transplant centres in the United Kingdom receive a proportion of their kidneys from other centres, the intended recipient having been carefully selected on the basis of tissue matching. Under these circumstances there is greater pressure to use the kidney since well-matched kidneys are hard to obtain.

We have both donated and received kidneys that have been damaged during removal. Sometimes the injury has been found only at the time of transplantation and some effort and ingenuity has been required to salvage the kidney and effect the transplant. In recording our experience with such kidneys, we would emphasise that we remain deeply obliged to the donating centres for the kidneys we have received.

Patients

137 renal transplants have been performed in this centre since 1967. 124 of these were first transplants, of which 117 were obtained from cadaver donors and 7 from relatives.

Arterial Injuries

Of the 137 transplanted kidneys, 113 had single renal arteries and anastomoses presented few difficulties. The artery of 1 kidney, however, had been damaged by undue traction and only a very short stump remained. It was anastomosed in the following manner. With the kidney surrounded by ice-cold saline, the hilum was turned uppermost and the stump of renal artery dissected out. 5 mm of artery was all that was remaining. The internal iliac artery of the donor was removed as a free graft and the distal end sutured to the renal artery using a continuous suture. The kidney was then transferred to the recipient where the proximal end of the internal iliac artery graft was sutured end to side to the external iliac artery. The kidney functioned soon afterwards and continues to perform well 3 months later.

Multiple renal arteries were present on 29 kidneys (21 %). The origins of these vessels had been included on an aortic patch in 9 cases and an anastomosis of the patch to the external iliac artery was readily achieved in each instance. A patch was not provided with the 20 other kidneys with multiple arteries and transplantation was more difficult. Two kidneys bore 2 renal arteries of equal size and in each case these were anastomosed individually to the external iliac artery. One kidney was rejected after 2 weeks but the other has functioned for more than 1 year.

18 kidneys were supplied with a main renal artery and a smaller polar vessel. Whenever possible an attempt was made to anastomose the polar vessel to some other artery. The techniques that were employed are shown in Figure 1. For lower polar vessels and vessels entering the hilum, we prefer to make an anastomosis to the inferior epigastric artery which is carefully preserved during the exposure of the iliac vessels of the recipient. 7 polar vessels were successfully anastomosed and 4 of these kidneys are currently functioning. 3 have been rejected. An arteriogram performed in 1 of these cases during an episode of rejection showed the polar vessel to be patent (Fig. 2). The polar artery could not be anastomosed in 11 cases and it was accepted that a portion of the kidney would become infarcted. In most instances the presence of a polar vessel was not suspected until the other anastomoses had been made and the kidney perfused with blood. A discoloured area of kidney then became visible and a careful search usually revealed a small stump of polar vessel entering the renal capsule. In these 11 cases, the area of kidney left ischaemic did not exceed one-sixth of the total. The outcome following transplantation may be seen in the Table. 8 of the 11 kidneys functioned, although 3 were subsequently rejected and another was lost when the patient died of a cardiac infarction. 3 kidneys never produced urine and when removed were found to have developed thrombus in the main renal artery. In 1 patient this may have been due to a technical factor, but in the other cases no obvious cause could be found. The current blood pressure in the surviving recipients is given in the Table. Although elevated, the values fall within the range observed in our transplanted patients who have not had renal infarcts.

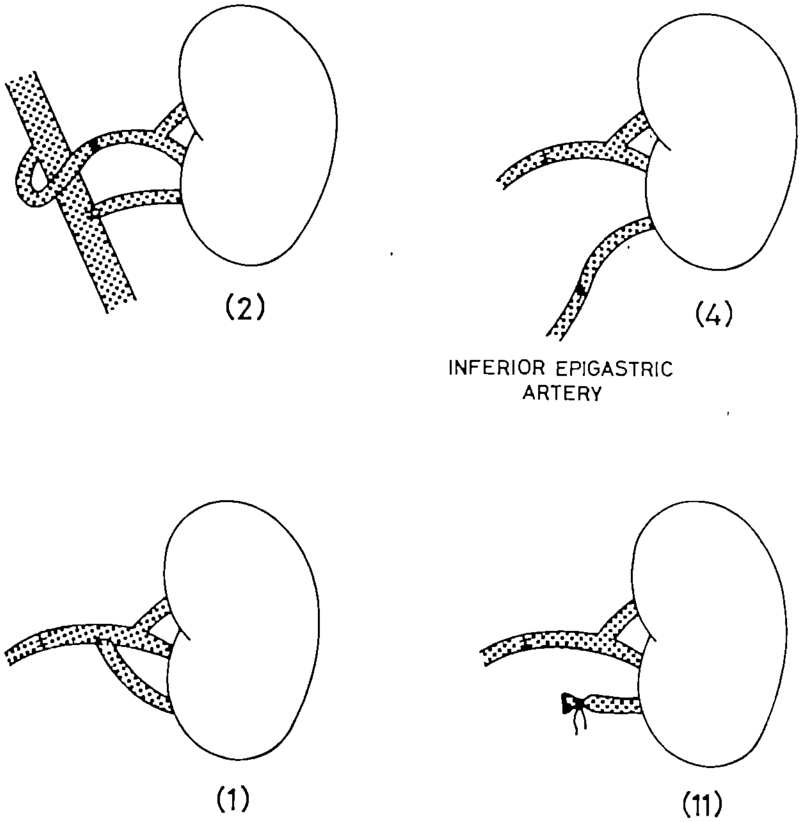

Fig. 1. Techniques that have been employed with kidneys bearing polar arteries devoid of an aortic patch. Numbers in parenthesis refer to the number of transplants treated in each way.

Venous Injuries

Damage to the main renal vein was uncommon but 1 vein required to be reconstructed. Traction on the vein had avulsed it almost completely but fortunately a large patch of vena cava had been provided with the kidney and from this a new renal vein was constructed (Fig. 3). The kidney is currently functioning well 2 months after transplantation. Where 2 large veins were provided on a patch of vena cava, both veins were preserved and the patch anastomosed to

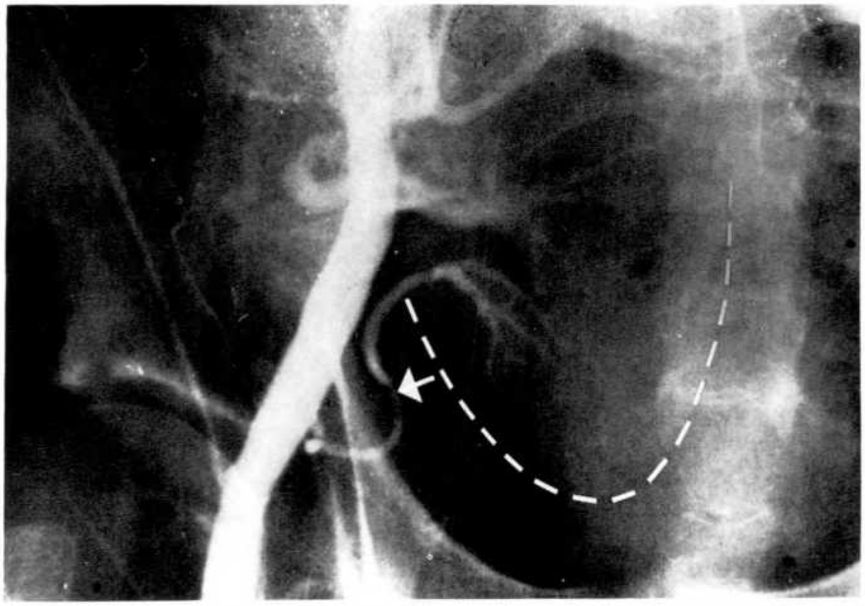

Fig. 2. Arteriogram showing a polar artery supplying the lower pole of a kidney transplant. It had been anastomosed to the inferior epigastric artery at the position indicated by an arrow.

Table

Functional Outcome of Kidneys transplanted with Unanastomosed Polar Arteries

Case No.	Infarcted Area	Present Status of Transplant	Present Blood Pressure
1	Upper pole	Functioning 2 years	140/90
2	Hilum	Functioning 1 year	160/100*
3	Upper pole	Functioning 9 months	150/100†
4	Upper pole	Functioning 8 months	140/100
5	Hilum	Removed. Rejection/urinary fistula	...
6	Lower pole	Removed, Rejection	...
7	Lower pole	Died. Rejection/CVA	...
8	Lower pole	Died. Cardiac infarction	...
9	Upper pole	Removed. Renal artery thrombosis	...
10	Lower pole	Removed. Renal artery thrombosis	...
11	Lower pole	Removed. Renal artery thrombosis	...

* Patient receiving Aldomet 1 g daily.

† Patient receiving Propanolol 40 mg daily.

the external iliac vein. Small accessory renal veins have been ligated without ill effect and one major tributary draining half a kidney was also ligated (on account of an injury) without any serious consequences developing. Venous infarction was observed, however, in one kidney where only 1 of 3 equal-sized renal veins was anastomosed. Although the venous drainage appeared adequate at the time of operation, the kidney did not function and renal vein thrombosis was discovered at the time of nephrectomy.

Ureteric Injuries

In the majority of cases the donor kidney was removed with an adequate length of well-vascularised ureter, but a few kidneys have been received with ureters measuring 4 inches or less. Although ureters of this length may not reach the base of the bladder as is required for a conventional anastomosis, they will generally reach the bladder vault, where it is our custom to implant ureters using the technique of Woodruff *et al.* (1969). The ureters of 2 kidneys had been accidentally divided close to the renal pelvis and in these cases the renal pelvis was anastomosed to the patient's own ureter. Both these kidneys are currently functioning well. Although we have encountered 6 ureteric fistulae in our series, we have not been able to attribute these to any ureteric injury or to stripping of the blood supply from the ureter at the time of removal.

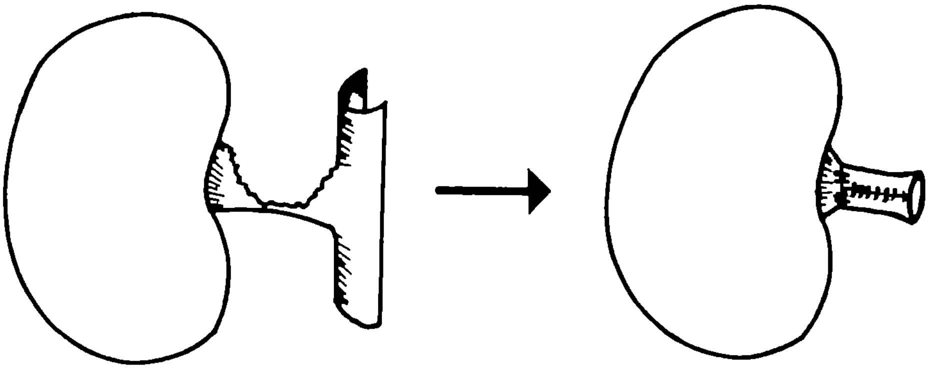

Fig. 3. Reconstruction of a torn renal vein with a segment of vena cava that had been provided with the kidney.

Discussion

The current shortage of cadaver kidneys and the difficulties in finding matched recipients make it imperative that kidneys should not be wasted. It is all too easy to damage a kidney during its removal and in the past such kidneys have been discarded. Our present policy is to make good the injury if at all possible and in this regard we have been moderately successful. Failure to anastomose a polar artery may have no serious consequences. 4 recipients are currently surviving with good renal function and with only a marginally raised blood pressure. Although it is well established that partial occlusion of a polar artery can cause hypertension (Brown *et al.*, 1960), total occlusion and infarction of part of a kidney may have only a transient effect (Benraad and Benraad, 1969). The hypertension that was present in these patients was no higher than that observed in our other recipients and the cause in both may be attributable to the side-effects of steroid therapy. Lower polar arteries supply blood to the ureter and therefore greater efforts should be made to anastomose these vessels. It is to be noted, however, that of the 11 kidneys that sustained infarcts, only 1 developed a urinary fistula and in that kidney the polar vessel had been supplying the hilum. 3 kidneys with polar infarcts subsequently developed thrombosis of the main renal artery. We find it difficult to explain why this should have occurred, although in 1 case the anastomosis may not have been performed satisfactorily. This complication has not been previously described.

Multiple renal veins have not presented many problems and because of free communications between them, all but the largest may be tied off (Smith *et al.*, 1962). Where 3 veins exist of equal size it might be wisest to anastomose 2, since venous infarction occurred in 1 transplant when only a single venous anastomosis was performed.

Although we have been able to salvage kidneys using the methods described, we believe that we should make greater efforts to prevent damage from occurring. The technique of nephrectomy is of no great relevance for kidneys have suffered injuries when removed *en bloc* as well as when removed individually. Careful, unhurried dissection of the renal vessels can be made only when the threat of ischaemic damage is removed, as is the case when the circulation is allowed to continue after the patient is pronounced cerebrally dead. Before one might remove kidneys under these circumstances a re-definition of death is required which would recognise cerebral death as an entity. These principles have already been accepted by countries in Europe and North America and we believe they now merit consideration in the United Kingdom.

Summary

Cadaver kidneys may be easily damaged during their removal from the donor. The current shortage of kidneys for transplantation makes it important that every kidney should be transplanted if at all possible.

In a series of 137 renal transplants, we have had to deal with 1 renal artery avulsion, 18 polar arteries devoid of aortic patches, 1 renal vein avulsion, multiple renal veins and 2 severed ureters. The manner in which these injuries have been dealt with is described.

As a means of preventing injuries in the future, it is suggested that the definition of death might be re-examined so as to permit the removal of kidneys from donors with an intact circulation.

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The Effect of Ubretid on Bladder Function after Recent Complete Spinal Cord Injury

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Ubretid (distigmine bromide) is an anti-cholinesterase compound with a prolonged action over a period of 12 to 24 hours (Hort, 1972) which has been found to be of use in the management of postoperative retention of urine, postoperative ileus, intestinal atony and as an adjuvant in the treatment of myasthenia gravis. Such an agent could possibly be of help in the early management of the bladder after spinal cord injury. This paper records the finding in serial investigations in 4 such patients in the first 6 to 12 weeks after injury. The results are here compared with those found in the control situation and those obtained with carbachol.

Patients and Method

Serial weekly investigations were made in 4 patients for the first 6 to 12 weeks after complete spinal cord injury.

Patients Studied

1. D. P., male, aged 35 years. Fracture dislocation D12/L1 from wall falling upon him (25.1.72). Sensory level L1. Bulbo-spongiosus reflex negative on admission (2 days after injury), positive at the time of investigation.
2. D. F., female, aged 31 years. Fracture dislocation C5/6 due to road traffic accident (19.1.72). Sensory level C5 on the left, C6 on the right. Anal reflex positive on admission (2 days after injury).
3. J. H., male, aged 27 years. Fracture dislocation D12/L1 whilst horse-riding (13.5.72), Sensory level D12. Bulbospongiosus reflex positive on admission (day of injury).
4. R. M., male, aged 47 years. Fracture dislocation D11/D12 due to an iron door falling across him (31.3.72). Sensory level L2. Bulbo-spongiosus reflex negative on admission (day of injury), positive at the time of investigation.

The studies included records of bladder pressure, the total volume of urine voided, and the residual urine at the end of each 2-hour tracing.

It has, for some years, been the practice of this unit to insert a suprapubic cannula to drain urine from the bladder in the early weeks after spinal injury before the patient is mobilised (Smith, Cook and Robertson, 1969). Initially a Bard 1966 suprapubic "Angiocath" was used, but because of kinking a change was made to Braun infant peritoneal dialysis catheters (distributed by Armour Pharmaceuticals Ltd) which have been very reliable.

The bladder pressure was measured through the cannula, and urine flowing from the urethra was collected by means of a condom appliance draining into a measuring cylinder with a transducer in its base. Bladder pressure changes and the volume of urine voided through the urethra were recorded using a 2-channel pen recorder (Devices M.2 pen recorder), with a strain gauge pressure transducer (Consolidated Electrodynamics Type 4-327 L221) to measure bladder pressure and a heavy-duty pressure transducer (Bell and Howell) to record urine volume. Both transducers were calibrated at the beginning of each investigation.

Tracings were taken for a minimum period of 2 hours. Control tracings were made on Mondays. On Wednesdays a trace was made in which carbachol 0·25 mg was given subcutaneously 15 minutes after the start of the recording and on Fridays a 2-hour recording was undertaken starting

8 hours after the injection of 0·5 mg of Ubretid intramuscularly, this being, according to the manufacturers, the time of maximum action of this drug. Further traces were also carried out for continuous periods of 8 and 24 hours to gain further information on the duration of action of Ubretid, the drug being given 30 minutes after the commencement of recording.

At the end of the 2-hour traces the bladder was emptied through the suprapubic cannula and the residual volume recorded. During the 8- and 24-hour tracings the bladder was emptied every 3 hours in those patients who were not passing urine per urethram and in those who were doing so the residual volume was determined at the end. During the 2-hour tracings each patient drank 1 litre of water and during the 8- and 24-hour tracings the patients drank water at the rate of 3 litres every 24 hours.

Table I

Control Series

Weeks after Injury	Maximum Pressure Change (cm H 20)				Volume Voided (mls)				Residual Urine (mls)			
	DP	DF	JH	RM	DP	DF	JH	RM	DP	DF	JH	RM
1	*	*	0	**	*	*	0	**	*	*	300	**
2	0	*	0	**	0	*	0	**	350	*	250	**
3	0	0	0	0	0	0	0	0	200	125	200	50
4	0	0	***	****	0	0	***	****	300	300	***	****
5	0	0	0	****	0	0	0	****	450	250	300	****
6	0	0	0	****	0	0	0	****	550	250	450	****
7	0	0	0	****	0	0	0	****	900	200	500	****
8	...	0	...	0	...	0	...	0	...	90	...	200
9	...	...	...	****	...	...	...	****	...	...	...	****
10	...	...	...	0	...	...	...	0	...	...	...	100
11	...	...	...	0	...	...	...	0	...	...	...	100

* Poor general condition, recordings not made.
** Fractured sternum, ribs, collapsed right lung and paraplegic ileus, recordings not made.
*** Pleural effusion and poor general condition, recordings not made.
**** Urinary infection—on continuous catheter drainage.

Results

The results obtained in the 4 patients are shown in the tables which record the maximum pressure change and the volume passed during the tracing and the residual urine volume at the end of each tracing.

In the control series (Table I) the bladder pressure remained constant throughout and no patient voided despite the presence of a considerable volume of residual urine. A sample control trace is shown in Figure 1.

In the patients who received carbachol (Table II) the bladder pressure always rose, usually by 30 to 60 cm of water. The contractions started within 2 to 10 minutes of injection, reached a peak in 2 to 5 minutes and fell gradually towards the base line over a further 30 to 50 minutes (Fig. 2). In all patients there was a fairly large volume of residual urine but urine was passed by only 1 patient who voided on 2 occasions. All tracings were similar and representative samples in 1 patient who failed to pass urine and in 1 of the patients who did so are shown in Figure 2, A and B.

In the patients receiving Ubretid changes in bladder pressure were less common and smaller in amplitude (Table III).

Following the administration of 0·5 mg of Ubretid intramuscularly 8 hours before the trace started, it was found that rhythmical bladder contractions could be seen as the bladder filled, the maximum pressure rise ranging from 10 to 60 cm of water. The contractions lasted from 1 to 5 minutes and recurred frequently; they did not, however, enable any subject to void urine despite considerable amounts of urine being present in the bladder. A representative trace is shown in Figure 3.

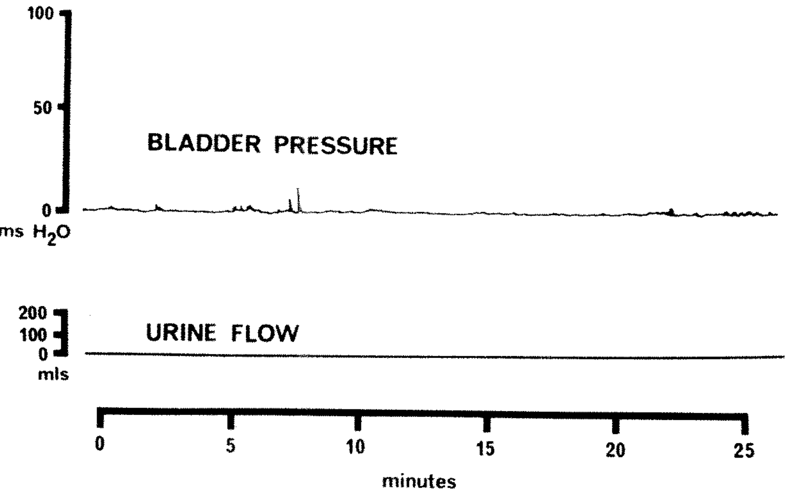

Fig. 1. Control tracing. Note constant bladder pressure and no flow of urine.

Table II

Results following Injection of Carbachol

Weeks after Injury	Maximum Pressure Change (cm H 20)				Volume Voided (mls)				Residual Urine (mls)			
	DP	DF	JH	RM	DP	DF	JH	RM	DP	DF	JH	RM
1	*	*	25	**	*	*	0	**	*	*	150	**
2	0	*	52	**	*	*	0	**	260	*	200	**
3	50	34	64	18	0	0	0	0	600	200	200	50
4	60	40	***	****	0	0	***	****	650	250	***	****
5	70	20	54	****	0	0	0	****	100	450	350	****
6	50	30	80	****	0	0	40	****	750	250	300	****
7	45	42	66	****	0	0	225	****	700	150	200	****
8	...	50	...	30	...	0	...	0	...	450	...	150
9	...	...	...	****	...	...	...	****	...	...	...	****
10	...	...	...	40	...	...	...	0	...	...	...	250
11	...	...	...	42	...	...	...	0	...	...	...	200

Key as for Table I.

24-hour tracings started immediately following the injection of Ubretid were carried out on 4 occasions in 2 patients. The bladder was emptied every 3 hours and, as above, the maximum pressure change, the volume passed and the residual urine volume were recorded (Table IV). The results showed a definite rise in bladder pressure, together with rhythmical contractions starting within 3 hours of injection, maximal at 9 to 18 hours, and thereafter falling towards the base-line. No patient passed urine despite a significant residual urine volume in each 3-hour period. No side-effects were noted after the administration of this drug.

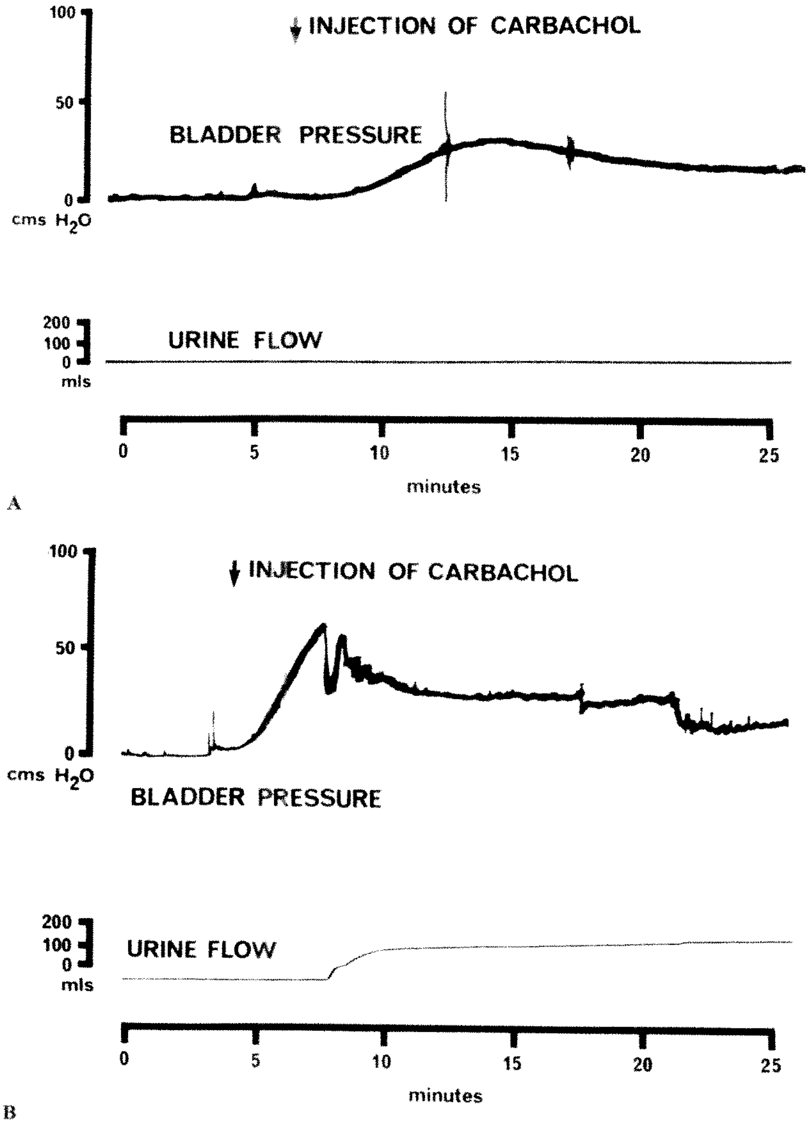

Fig. 2. A, Tracing following carbachol. Note the rise in bladder pressure in the upper tracing and the absence of flow in the lower tracing. B, Tracing following injection of carbachol in which the patient voided.

Discussion

Micturition involves detrusor contraction with pelvic floor relaxation. The process is reflex, is co-ordinated by the centres in the mid-brain and is under voluntary control. After spinal cord injury with paraplegia the nervous pathways governing this reflex are interrupted and as a result

Table III

Results following Injection of Ubretid

Weeks after Injury	Maximum Pressure Change (cm H 20)				Volume Voided (ml)				Residual Volume (ml)			
	DP	DF	JH	RM	DP	DF	JH	RM	DP	DF	JH	RM
1	*	*	0	**	*	*	0	**	*	*	390	**
2	0	*	15	**	0	*	0	**	600	*	150	**
3	0	0	15	0	0	0	0	0	750	200	250	250
4	0	0	***	****	0	0	***	****	700	325	***	****
5	0	0	15	****	0	0	0	****	350	150	400	****
6	0	0	45	****	0	0	0	****	750	90	400	****
7	0	0	60	****	0	0	0	****	550	250	200	****
8	...	0	...	0	...	0	...	0	...	250	...	200
9	...	...	...	****	...	...	...	****	...	...	...	****
10	...	...	...	20-25	...	...	...	0	...	...	...	250
11	...	...	...	48	...	...	...	0	...	...	...	650

Key as for Table I.

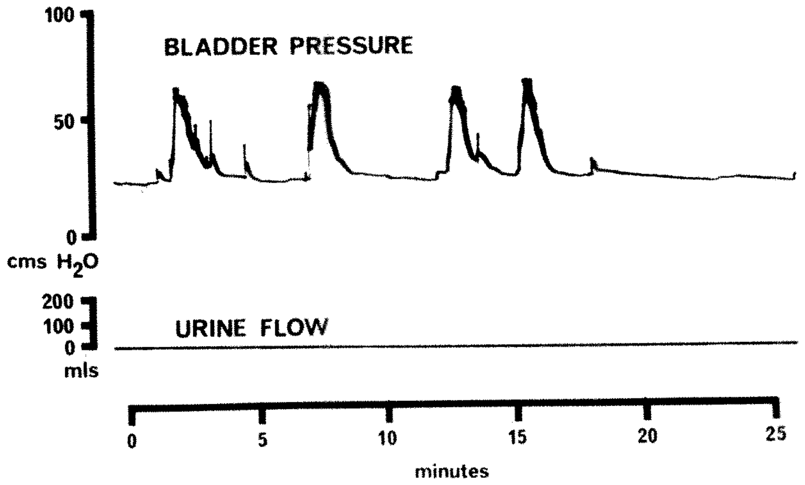

Fig. 3. Tracing between 8 and 10 hours following the injection of Ubretid. Note rhythmical change in bladder pressure without urine flow.

Table IV

Results of 24-hour Traces following Injection of Ubretid

Name	Weeks after Injury	Maximum pressure Change (cm H 20) Time in hours)								Volume Voided (ml) (Time in hours								Residual Urine (ml) (Time in hours)							
		3	6	9	12	15	18	21	24	3	6	9	12	15	18	21	24	3	6	9	12	15	18	21	24
J. H.	5	15	10	20	10	18	10	12	15	0	0	0	0	0	0	0	0	400	300	300	200	200	200	300	330
J. H.	6	15	20	52	30	24	40	32	40	0	0	0	0	0	0	0	0	400	400	500	400	175	100	400	750
J. H.	7	10	24	36	30	14	60	60	...	0	0	0	0	0	0	0	...	200	300	170	150	150	300	200	...
R. M.	11	32	48	40	40	40	52	40	30	0	0	0	0	0	0	0	0	650	275	400	300	175	100	200	200

detrusor contraction becomes weak, ill-sustained and inefficient, whilst, after the first few weeks, spasm of the striated muscles of the pelvic floor and external sphincter further complicates the picture by increasing the urethral resistance.

During the first few weeks after injury the bladder is drained by an intermittent or continuous technique and attempts are made to persuade the patient to void urine. It was hoped that Ubretid would be of assistance in this difficult period.

The action of Ubretid was compared with the control situation and with that following the injection of carbachol.

From the findings it would seem that in this series the bladder was inactive in the first 12 weeks after spinal cord injury. The injection of carbachol will rapidly raise the intravesical pressure and may cause urine to flow; and an injection of Ubretid will also cause a rise in bladder pressure with rhythmical bladder contractions, but does not seem to assist the patient to empty the bladder.

No patients with true cauda equina lesions (showing a persistently negative bulbo-spongiosus reflex) have, as yet, been studied.

Conclusions

There is no evidence from these recordings that Ubretid has a significant place in the management of the bladder in the early weeks after spinal cord injury especially as, in our view, it is more desirable, at least in patients with complete paraplegia, to decrease the urethral resistance than to increase the bladder pressure.

Summary

Recordings of bladder pressure and urine flow have been carried out in 4 patients in the early weeks after spinal cord injury in the control situation, following the injection of 0·25 mg carbachol, and after injection of 0·5 mg Ubretid.

In the control situation the bladder pressure remains constant and low.

Following the injection of carbachol there is a predictable rise in the bladder pressure of 30 to 60 cm of water which gradually falls towards the base line after 30 to 50 minutes and, on occasions, is associated with a flow of urine.

After the injection of Ubretid the basal bladder pressure rises and rhythmical contractions occur, of 10 to 60 cm of water in maximum height but in no case did this assist the patient to void urine.

In our view Ubretid is not indicated in the management of the bladder in early weeks after spinal cord injury.

We should like to acknowledge the help of the Medical Illustration Department at Leeds (St James's) University Hospital in the preparation of the illustrations and the generous help of Berk Pharmaceuticals Ltd.

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The Genito-urinary Manifestations of Herpes Zoster

Three Case Reports and a Review of the Literature

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Herpes zoster (zoster) is an infection by the varicella virus in a partly immune person and 70% of patients give a previous history of chickenpox. The virus proliferates in the dorsal root ganglion causing an inflammatory reaction characterised by nerve cell necrosis, haemorrhage and a mononuclear infiltration. The fibres of the related nerve root and nerve show similar changes and the inflammatory reaction can spread proximally to involve the spinal cord and anterior horn cells. The cutaneous vesicle shows a unilocular ballooning degeneration of the deeper epidermal layers with nuclear inclusions present in the giant cells and in the epidermal cells (Downie, 1967; Rhodes and van Rooyen, 1968).

Three cases of zoster affecting different segments of the spinal cord and resulting in urinary retention are presented.

Case Reports

Case 1. Miss A. B., a spinster aged 74, was admitted on 30.7.1971 with urinary retention. Six days prior to admission she developed a painful vesicular eruption involving the perineum and right buttock. Micturition became increasingly difficult. On examination she was ill and dehydrated, the bladder was distended and there was a typical zoster rash involving the right buttock and perineum. There was no neurological deficit. 950 ml of turbid urine were drained on catheterisation.

Investigations. Hb: 13·8 g %; W.C.C.: 6,700 per cu.mm; E.S.R.: 25 mm in 1 hour; Blood urea: 103 mg %; C.S.U.: excess of W.B.Cs. only. I.V.P. Normal. Cystoscopy performed after 8 days showed an area of ulceration on the right lateral bladder wall. Cystometry showed a large capacity atonic bladder (Fig. 1).

Constipation was a recurrent problem and required repeated enemata. The patient voided urine spontaneously after 13 weeks of catheter drainage. Subsequent follow-up showed that she was passing urine normally.

Case 2. J. B., male, aged 68 years, was admitted on 22.4.1972 with urinary retention. Five days prior to admission he had developed severe bilateral girdle pain over the 10th thoracic dermatomes. He complained of generalised lower limb weakness and paraesthesiae. Micturition became increasingly difficult and he was constipated. On examination the bladder was distended and there was a vague and tender, macular and bilateral rash over the 10th thoracic dermatomes. Neurological examination revealed only bilateral extensor plantar responses. 700 ml of urine were drained on catheterisation.

Investigations. Hb: 16·1 g %; W.C.C.: 6,400 per cu.mm; Blood urea: 45 mg %; C.S.U.: sterile; C.S.F.: 92 lymphocytes; Protein: 28 mg %; Sugar: 50 mg %. I.V.P. normal. Cystoscopy showed normal appearances; no bladder neck obstruction. Rectal examination: small benign prostate. Cystometry: normal sensation and capacity (Fig. 2).

The rash faded after 1 week with improvement in both subjective and objective neurological findings. After 2 weeks the catheter was removed and spontaneous micturition followed. At follow-up examination in 1 month the patient was asymptomatic.

Case 3. M. C., male, aged 68 years, was admitted on 16.6.1972 with urinary retention. Three weeks prior to admission he had developed a classical zoster eruption involving the 2nd and 3rd lumbar dermatomes on the left side. One week prior to admission he had become constipated and micturition proved increasingly difficult. On examination he was an ill, dehydrated patient with a distended and tender bladder. A typical zoster rash on the anteromedial aspect of the left thigh was present. 1,000 ml of urine were drained on catheterisation.

Investigations. Hb: 13·1 g %; W.C.C.: 6,000 per cu.mm; E.S.R.: 53 mm in 1 hour; Blood urea: 58 mg %; C.S.U.: sterile; C.S.F.: 17 cells/pf; Protein: 65 mg %; Sugar: 70 mg %. I.V.P. normal. Virology: zoster titre 1 : 8 to 1 : 250 in 2 weeks. Cystoscopy: normal appearances with no bladder neck obstruction, rectal examination—small benign prostate, cystometery: normal sensation and capacity. (Fig. 3).

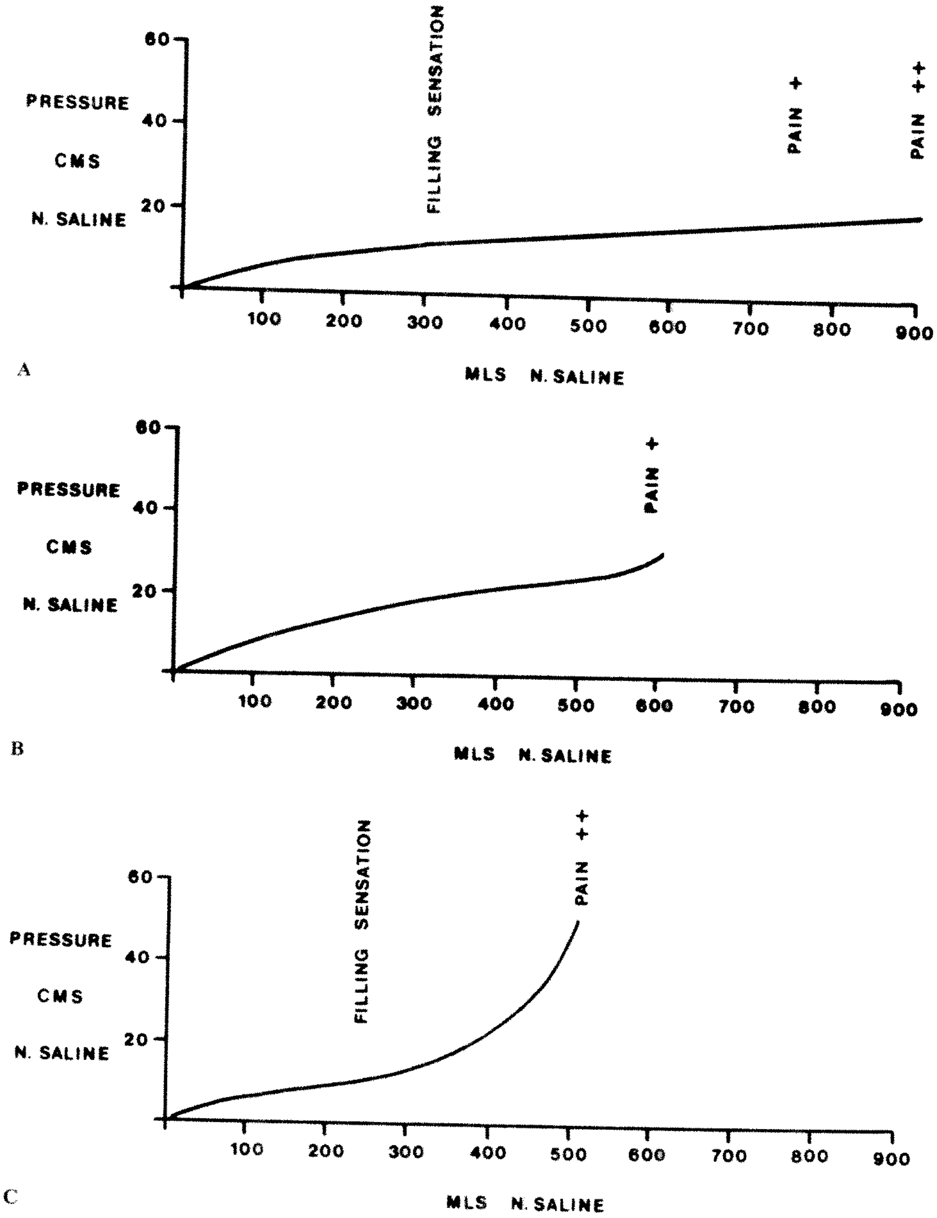

Fig. 1. A, B and C, Serial cystometrograms of case 1 (A. B.).

The rash slowly resolved and the catheter was removed after 10 days. Normal micturition was resumed after a single intramuscular dose of carbachol. At follow-up the patient was asymptomatic.

Comment

The genito-urinary manifestations of zoster can be classified into a syndrome of cystitis-like symptoms and one where urinary retention occurs (Table I).

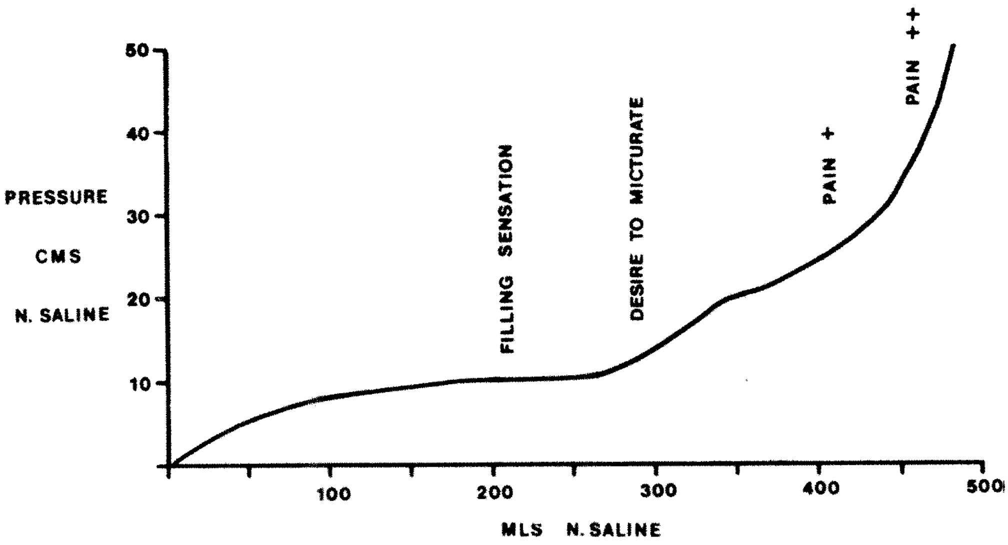

Fig. 2. Cystometrogram of case 2 (J. B.).

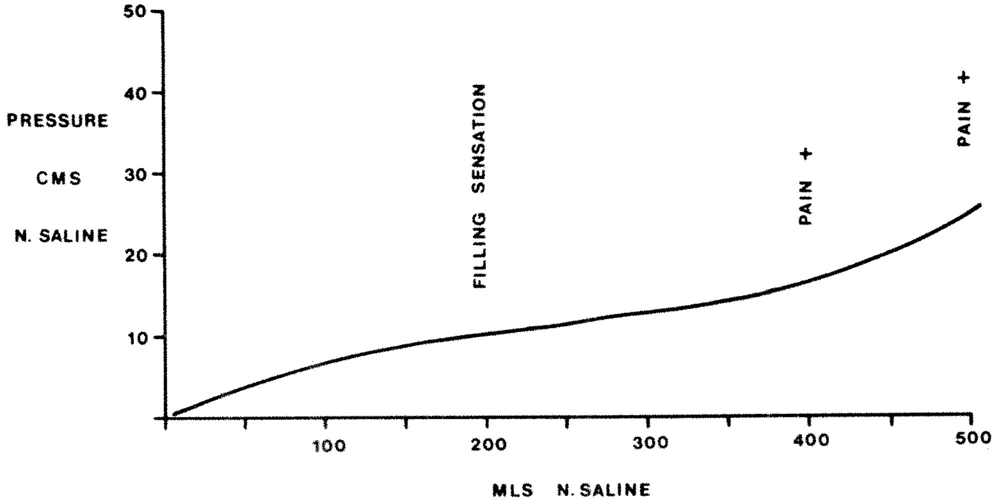

Fig. 3. Cystometrogram of case 3 (M. C.).

Zoster cystitis can present with dysuria, frequency or haematuria. The virus affects the dorsal root ganglia of either the thoraco-lumbar or sacral cord segments and travels via the autonomic nerves to the bladder. The characteristic zoster eruption of local erythema, oedema and vesicle formation results and it is this lesion which is responsible for the symptoms in zoster cystitis. At the same time a zoster eruption is found involving the relevant cutaneous dermatome.

Table II gives the proportions in which the thoraco-lumbar (T10 to L3) and sacral cord segments are involved and it can be seen that in a majority of cases the thoraco-lumbar region is

Table I

Details of Previously Reported Cases

Date	Author	Level	Age	Sex	Symptoms, etc.
1890	Davidsohn	Sacral	62	M	Retention
1902	Curtin	Th. 10	?	M	Haematuria
1903	Rouyer	Sacral		?	Cystitis
1909	Tomey	L1/2/3	35	M	Cystitis
1909	Siding	L1	72	F	Cystitis
1910	Parsat	Sacral	?	M	Retention
1911	Oppenheim	Sacral	?	?	Retention
1913	Volk	Sacral	?	M	Dysuria
1913	Frankl-Hochwart	Sacral	?	M	Dysuria
1913	Van De Scheer	D10	56	F	Frequency
1925	Spitzer	L1/2/3	?	M	Dysuria
1926	Schniffman	Sacral	31	F	Retention
1926	Dubois	Sacral	40	M	Retention, Cysto. Pos.
1929	Darget	L1	65	F	Cystitis. Cysto. Pos.
		No rash	?	F	Cystitis. Cysto. Pos.
1931	Mann	Sacral	31	F	Cystitis
1932	Chesterman	S1/2/3	64	F	Cystitis
1939	Gais Abrahamson	6 cases of zoster with cystitis			
1941	Rinker	No rash	45	M	Cystitis
1946	Ford	Abdo	?	?	Cystitis
1948	Watt	L3	34	M	Cystitis
1950	Leca	Sacral	52	F	Cystitis. Cysto. Pos.
		Sacral	53	F	Retention
1955	Lerman/Millstein	Sacral	42	M	Retention
1955	Zachariae	Sacral	54	M	Retention
1956	Thompson	Sacral	61	M	Retention
1956	Gibbon	Sacral	57	M	Retention. Cysto. Pos.
1956	Dales/Wilson	L/2	42	M	Retention
1957	Wyburn Mason	D11-L1	62	F	Cystitis. Cysto. Pos.
		D12-L2	56	M	Cystitis. Cysto. Pos.
1957	Jeanneret/Delacretez	Sacral	20	F	Retention
1959	Meyer	Sacral	70	F	Retention. Cysto. Pos.
		Sacral	76	F	Retention
1962	Berghaus	Sacral	64	M	Retention
		Sacral	63	M	Retention
1962	Ristic/Gospavic/Til	Th. 2/3	58	M	Retention
1963	Burke	Sacral	60	M	Retention. Cysto. Pos.
1964	Golubev	Th. 10	32	M	Cystitis. Cysto. Pos.
1964	Harrison	Th. 6/7	69	M	Retention
1964	Pendharkar	Th. 5	34	M	Retention
1967	Weber/Wolfram	Sacral	65	F	Retention. Cysto. Pos.
1967	Gernert	Sacral	73	M	Retention
1969	Rankin/Sutton	Sacral	70	M	Retention
		L1/2	25	F	Retention
1969	Constantian	Sacral	37	F	Retention
		Sacral	79	M	Retention
1970	Ray, Wise	Sacral	61	M	Retention
1970	Yachika	Sacral	69	M	Retention

Yachika in reviewing the Japanese literature reports on cases of zoster with urinary symptoms. Ten had zoster cystitis, 6 presented with retention. All the cases of zoster cystitis had confirmatory cystoscopic findings. These cases are included in the comments.

affected. Table III shows that zoster cystitis occurs predominantly in males with a mean age of 33 years compared with 50 years in females.

All the reported cases of zoster cystitis were managed conservatively with symptomatic treatment. The disease ran a short course and there was no residual disability.

Involvement of the bladder mucosa was discovered endoscopically in 17 cases whereas the typical eruption was found only in 6 cases with zoster retention. It was Gibbon (1956) who postulated that there was an inverse relationship between the severity of the bladder eruption and urinary retention. This indicates that another mechanism must be responsible for the development of urinary retention.

Table II

Cord Level Involvement in Zoster Cystitis

Level	Number	
Thoracolumbar	12	66%
Sacral	6	33%
Total	18	100%

Table III

Age/Sex Incidence in Zoster Cystitis

Sex	Number		Age (mean)
Male	19	68%	17-56 yrs (33)
Female	9	32%	18-64 yrs (50)
Total	28	100%	

Table IV

Cord Level Involvement in Zoster Retention

Level	Number	
Sacral	25	78%
Thoraco-lumbar	4	11%
High thoracic	3	11%
Total	22	100%

Table V

Age/Sex Incidence in Zoster Retention

Sex	Number		Age (mean)
Male	24	75%	40-79 (58)
Female	8	25%	20-76 (57)
Total	32	100%	

Patients who develop zoster urinary retention present firstly with a typical rash followed by a period of increased difficulty in micturition. In these cases it is suggested that the inflammatory reaction commencing in the dorsal root ganglia by spreading proximally and distally interferes with the autonomic motor supply to the bladder, so disturbing the voiding mechanism.

It is the proximal spread of the inflammatory reaction to involve the cord which accounts for the bilateral depression of the spinal reflex where only a unilateral cutaneous lesion is present (Gibbon, 1956).

Table IV shows that the sacral cord segments are predominantly affected; involvement of the parasympathetic outflow from this part of the cord presumably is responsible for the urinary retention.

Evidence to support this suggestion is given by the cystometrogram in case 1 (Fig. 1) where a large capacity atonic bladder was found. Yachika (1970) reported similar findings.

A second category of zoster retention is found when the upper thoracic cord segments are involved. Our case (J. B.), with zoster affecting the 10th thoracic segments bilaterally, developed a transverse myelitis. This was confirmed by the presence of subjective and objective lower limb neurological signs and a high lymphocyte count in the cerebrospinal fluid. Pendharkar (1964) presented a similar case. The urinary retention which results is probably due to interference with cortical control of micturition due to disturbance of the long tracts.

The third group of patients are those who develop retention of urine when zoster affects the thoraco-lumbar cord segments. It is more difficult to explain the mechanisms of urinary retention in these cases.

It is known that because of its embryological origins the trigone receives a motor innervation from the sympathetic outflow and this is confirmed by histochemical studies (Ramsdale, 1972). Thus if paralysed by zoster involvement of its motor supply the trigone would be unable to initiate micturition by contracting and funnelling open the bladder neck (Tanagho, Meyers and Smith, 1968). But as urinary retention is not a feature of either surgical or chemical sympathectomy other factors must be present.

Abdominal wall paralysis of some degree must occur when the thoraco-lumbar cord segments are involved by zoster and this could affect the initiation of micturition. The zoster rash is exquisitely painful and this could play a role in the development of urinary retention.

Disturbance of the integrated micturition reflexes (Barrington, 1931) mediated by both autonomic and somatic reflex arcs may also be a causal factor.

We are unable to explain satisfactorily the mechanisms of urinary retention when zoster affects the thoraco-lumbar cord segments.

In the management of these previously reported cases the following regime was carried out. Routine clinical examination was followed by aseptic catheterisation. A haematological and biochemical base-line was obtained and after excretion urography, cystoscopy was performed to exclude or confirm the presence of a zoster eruption. At the same time the bladder neck was assessed with regard to outflow obstruction. One case (A. B.) had a definite localised area of inflammation and in neither of the male patients was there any degree of bladder neck obstruction. Both of these patients passed urine spontaneously on removal of the catheter after the rash had begun to fade. As zoster retention occurs at a mean age of 58 years (Table V) in males, a time when prostatism becomes increasingly common, it is important to note that normal micturition has always occurred after catheter removal on resolution of the rash. In 1 or 2 reported cases (Gibbon, 1956) perurethral resection has failed to relieve the urinary retention.

Serial cystometry is of help to give some indication of resolution of the pathological process and this can be seen comparing the cystometrograms of patient A. B. (Fig. 1, A, B and C). Cystometry is of particular use when the sacral cord segments are involved.

Serial viral studies will confirm the clinical diagnosis of a zoster infection.

Lumbar puncture and cerebrospinal fluid analysis does give valuable evidence of spinal cord involvement when a transverse myelitis is thought to be present (see case J. B.).

Continuous catheter drainage was used and the catheter was removed at intervals and reinserted if there was any significant residual urine. Our first case (A. B.) required 13 weeks of continuous drainage, and the repeated use of carbachol failed to alter the course of events.

Constipation was a problem in all 3 of our cases and other authors reported similar findings. Regular aperients and enemata were required.

Summary

Three cases of herpes zoster involving different spinal cord levels causing urinary retention are presented.

Review of the literature has revealed similar cases and a separate syndrome of zoster cystitis.

In the light of our reported cases and others previously recorded the neuropathic mechanisms are discussed and a scheme of management is described.

I am grateful to Mr J. B. Garland for allowing me to report these cases which were under his care and his advice in the preparation of this paper. I am also grateful to Miss Perry of Crumpsall Hospital, Photographic Department, and Mr R. A. Simpson for preparation of the photographs and figures. I am indebted to Mrs B. Lingard for preparation of the manuscript.

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Carcinoma of the Urinary Tract and Urinary Retention in Uganda

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The aetiology of most human urinary cancer remains unknown. It is reasonable to postulate, however, that whatever causes cancer in the urinary tract reaches it from the urine (Hueper, 1969). This is supported by the fact that malignancy arises most commonly in the bladder, where urine remains in contact the longest. Obstruction to the flow of urine should enhance the action of any carcinogen that may be present. Dodge (1964) has drawn attention to this when he reported a high frequency of urethral strictures in Ugandan African patients with carcinoma of the bladder. A similar finding was also reported from Jamaica by Weston (1961*a*) and Atkinson (1967). In Europe, Perelman and Schabad (1963) found evidence of urinary obstruction in the form of prostatic enlargement, diverticula and stones in 92 (65·7%) of 140 male patients with carcinoma of the bladder, but this has not been a general experience.

It is of interest that an unduly high proportion of tumours in Uganda and Jamaica were squamous cell carcinomas. This histological type is commoner in most parts of the tropics and subtropics than in the temperate zones and it has long been assumed that this is due to a high prevalence of *Schistosoma haematobium* infestation. These data have been recently reviewed by Clayson and Cooper (1970). A relationship between squamous bladder cancer and urinary schistosomiasis undoubtedly exists but may not necessarily be a directly aetiological one and could operate through urinary retention, secondary infection and other means. Dodge (1964) as well as Weston (1961*a*) and Atkinson (1967) have commented on the rarity of schistosomiasis in the areas they studied.

In the years 1970 to 1972 an extensive survey of all forms of cancer was carried out in Uganda based on material collected by the Kampala Cancer Registry in the 5-year period 1964 to 1968. During these years an exceptionally high level of registration and documentation was achieved due to full staffing, enthusiastic clinical cooperation and a country-wide histological diagnostic service. This gave the opportunity to examine in detail the pathology of urinary tract cancer, the role of urinary retention and of other possible factors, including schistosomiasis.

The Land and People of Uganda

Uganda is a small country with a surface area of approximately 75,000 square miles of land and a further 20,000 square miles of lakes, of which Victoria is the largest. It lies astride the equator mostly at a level of around 4,000 feet. The climate is equable with average midday temperatures of 70° to 80°F. throughout the year, abundant sunshine and plentiful rain in the form of frequent tropical downpours. The vegetation is luxuriant. The population in 1959 was 6,449,000 and in 1969 9,451,000. For the purpose of this study calculations were based on the mid-point of the 5-year period 1964 to 1968. The majority of the inhabitants belong to a Bantu tribe called the Baganda who occupy the lush, fertile land of the plateau. This was once the powerful independent Kingdom of Buganda and is still the most advanced part of the country culturally and economically. Urban civilisation is centred on the capital, Kampala. Approximately 95% of Ugandans are rural dwellers engaged in the production of basic foodstuffs, of which steamed green bananas (matoke) form the main bulk. Manufacturing industry is in its infancy. Medical facilities are well developed and cover the entire country through an interlocking system of Government and missionary hospitals, dispensaries and mobile clinics. There is one medical school, Mulago Hospital, located at Makerere University in Kampala. The Cancer Registry was set up in 1954 and registration has covered the whole country since 1961.

Material

The histology and clinical records of all cases of carcinoma of the urinary tract registered in the Kampala Cancer Registry during the 5-year period 1964 to 1968 were reviewed. 184 cases were found acceptable. The diagnosis was made on biopsy in 153 cases and at postmortem in 31. The distribution by site and histological type is summarised in Table I. Anaplastic tumours of uncertain origin and other, non-epithelial, tumours were excluded from further study. Sections were cut and stained by routine histological methods.

Table I

Carcinoma of the Urinary Tract in 184 Uganda Africans: Distribution by Site and Histological Type

	Renal Pelvis	Bladder	Urethra	Total
Squamous cell carcinoma	2	75	38	115
Adenocarcinoma	...	26	3	29
Transitional cell carcinoma	2	19	1	22
Anaplastic carcinoma	...	7	...	7
Other	...	11	...	11
Total	4	138	42	184

Results

Incidence, Age and Sex

The total incidence rate per 100,000 per year of carcinoma of the renal pelvis, bladder and urethra in Uganda during the 5-year period of study was 4·6 for males and 0·9 for females. This rate is about average when compared with incidence rates from many cancer registries throughout the world (Doll, Payne and Waterhouse, 1966). 126 (68·4%) of 184 cases occurred in Buganda, of which 106 were Baganda and 20 were of other immigrant tribes. This apparent concentration of cases in the most urbanised part of the country is unlikely to be due solely to selection by availability of hospital diagnostic facilities, as these exist throughout the country. A possible source of bias is the existence of sophisticated urological skill and, in particular, diagnosis by cystoscopy both of which tend to be concentrated in the main Kampala hospitals. Many cases, however, presented with such gross disease that the correct diagnosis was obvious on simple clinical examination.

The age and sex incidence is shown in Figure 1. The youngest patient was 20 and the oldest 95 years of age, but the majority fell in the 40 to 70 age-group with a mean of 54·8 years. Males predominated over females to quite an unusual extent, the ratio of male to female being 8·1 : 1.

The overall incidence, age and sex distribution were similar for all 3 sites shown in Table I.

Clinical Presentation

One of the 4 renal pelvic tumours was associated with nephrolithiasis which was discovered in the course of investigations for renal colic. About one-third of the patients with tumours of the bladder and the urethra gave a clear history of difficulty in micturition for up to 20 years. Many were known to have posterior urethral strictures and to have had relief by suprapubic cystostomy and catheterisation. Patients frequently presented with pelvic involvement or tumour fungating through lower abdominal and perineal fistulae and, in 8 cases, through cystostomy tracts. Prognosis was poor, many were lost to follow-up and were presumed to have died of their disease.

Pathology

The pathological findings will be presented separately for each of the 3 sites.

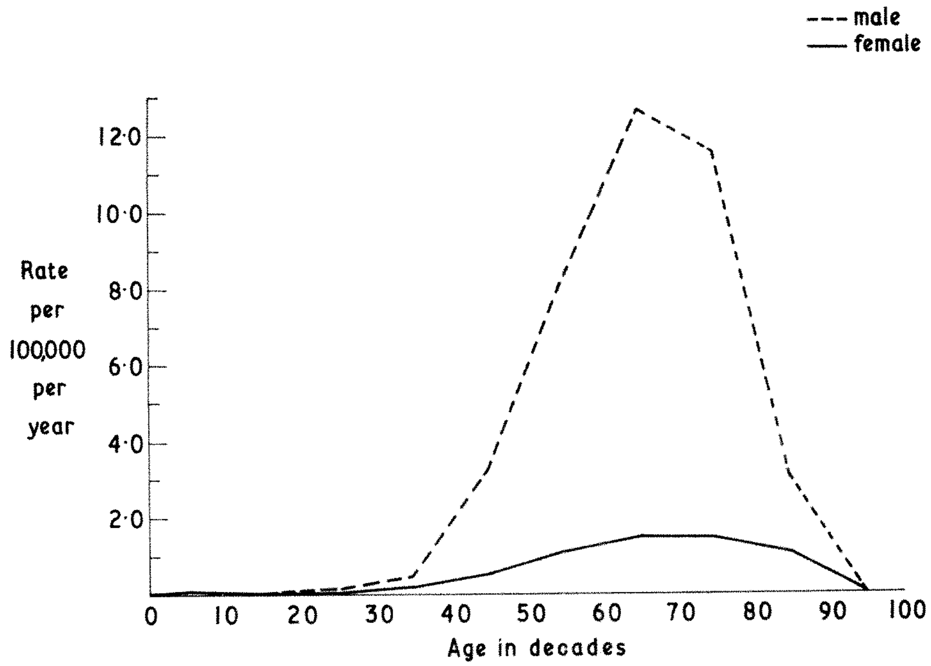

Fig. 1. Age and sex distribution of 184 cases of urinary tract cancer in Uganda.

Renal pelvis: 4 cases, 2 of which were squamous cell carcinomas and 2 were transitional cell carcinomas. One of the former was associated with stones in the renal pelvis, the only case of urolithiasis in the entire series.

Bladder: 120 cases (excluding 7 anaplastic tumours of uncertain origin and 11 non-epithelial tumours). Information on the site of the tumour was available in 86 cases. The whole of the bladder was involved in 35 (40%), the trigone in 33 (38%), the lateral walls in 14 (16%) and the fundus in 2 (3%). The tumour arose from multiple sites in 2 cases (3%). In only 9 of these 86 cases was the tumour still confined to the bladder wall. As Table I shows, 75 (62·5%) of these 120 cases were squamous cell carcinomas. Over two-thirds were well-differentiated, keratinising tumours (Fig. 2) forming ulcerated, shaggy masses. The next commonest histological type was adenocarcinoma with 26 cases (21·7%). These formed an interesting group with varied features which will be reported elsewhere. The majority (18 cases) were of intestinal type, 4 were papillary growths with a surface lining of cuboidal cells in a peg-like arrangement resembling mesothelium and 4 tumours were made up of clear cells forming structures reminiscent of mesonephric tissue. The least common histological variant was transitional cell carcinoma: 19 cases (15·8%). Seven of these showed patchy squamous metaplasia.

Urethra: 42 cases, giving a bladder: urethra cancer ratio of 3 : 1. As Table I shows, 38 (90·4%) were of the squamous cell type. All but 3 arose from the posterior urethra where they formed indurated perineal swellings. These tumours spread into the urethral bulb first (8 cases), then to the perineum (20 cases), base of penis (6 cases), scrotum (5 cases), buttocks (1 case) and inguinal lymph nodes (16 cases).

Schistosomiasis

No eggs were found in the urine and in none of the histological material examined was there any evidence of schistosomal infestation.

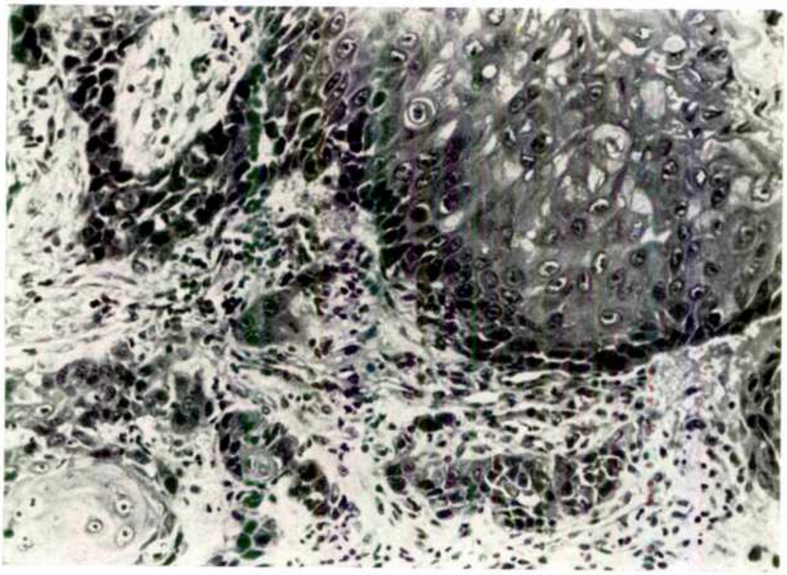

Fig. 2. Well-differentiated squamous cell carcinoma of the bladder. Haematoxylin-eosin. × 160.

Urethral Strictures

Both bladder and urethral carcinomas were associated with urethral strictures, as shown in Table II. The highest proportion was found in squamous cell carcinoma closely followed by adenocarcinoma and the lowest in transitional cell carcinoma. All these strictures were situated in the posterior urethra in males the majority of whom gave a history consistent with gonorrhoea many years past. Patients with strictures were, on average, 6 years younger than those without strictures.

Metaplastic Changes in Non-tumourous Mucosa

Histological material away from the tumour was available in 51 cases of bladder carcinoma. As Table III shows, squamous or glandular metaplasia and carcinoma-in-situ were present in a high proportion (25 of 51, or 49%). Excepting 4 cases of squamous cell carcinoma, all were associated with strictures.

Discussion

The pattern that emerges from this study is that of a high frequency of squamous cell carcinoma of the bladder and urethra not associated with urinary schistosomiasis but with posterior urethral strictures. Males were found to predominate to an unusually high degree and patients with strictures were slightly younger than those without strictures. The population at risk is a tropical farming community with a high dietary intake of carbohydrate, particularly bananas.

A high frequency of squamous cell carcinoma of the bladder has been reported from Egypt (Dimmette, Sproat and Sayegh, 1956), Portuguese East Africa (Gillman and Prates, 1962), South Africa (Oettlé, 1955), Jamaica (Weston, 1961*a*; Atkinson, 1967) and, in a previous study, from Uganda (Dodge, 1962). This is in contrast to England (Pugh, 1959) and North America (Mostofi, 1968), where squamous cell carcinoma is rare. Adenocarcinoma is also commoner in Uganda than in the temperate zones where its frequency is no more than 1 to 2% and where it is usually found in association with exstrophy of the bladder. By contrast, transitional cell tumours which account for the vast majority of urothelial tumours in most parts of the world form only a minority in Uganda. It may well be that squamous cell and adenocarcinomas and transitional cell carcinoma form 2 distinct groups with different aetiologies or that secondary factors operate to modify the tissue response. The importance of registering bladder cancer by histological type for epidemiological purposes has recently been emphasised by Tulinius (1970).

Table II

Carcinoma of the Bladder and Urethra: Proportion of Patients with Urethral Stricture in the Three Main Histological Types

	Bladder (%)	Urethra (%)
Squamous cell carcinoma	32 of 75 (42·6)	20 of 38 (52·6)
Adenocarcinoma	9 of 26 (34·6)	1 of 3 (33·3)
Transitional cell carcinoma	2 of 19 (10·5)	0 of 1 (0)
Total	43 of 120 (35·8)	21 of 42 (50)

Table III

Carcinomas of the Bladder: Changes in Non-tumourous Mucosa in the Three Main Histological Types

	No.	Metaplasia	Carcinoma-in-situ
Squamous cell carcinoma	38	13*	7
Adenocarcinoma	4	4†	...
Transitional cell carcinoma	9	1*	...
Total	51	18	7

* Squamous metaplasia.
† Glandular metaplasia.

Table IV shows, in a summary form, a number of seemingly disparate factors that have been incriminated in the aetiology of cancer of the urothelium in man.

Chemical carcinogens of industrial origin, the importance of which is well established in Western countries, are unlikely to have any significant role in Uganda. 95% of the population live off the land and the type of industrial activity such as the manufacture of dyestuffs, rubber or insulating materials hardly exists even in the capital. The evidence for smoking as an aetiological factor is slowly accumulating, but this is a recently acquired habit in Uganda and consumption is still low. Other diseases such as carcinoma of the lung, coronary disease and chronic bronchitis in which smoking has a much more important causative role are all rare. It may be added that in countries where exposure to industrial carcinogens and smoking are common, cancer of the urothelium is predominantly of the transitional cell type.

The high frequency of squamous cell carcinoma in Uganda raises the question whether this might be causally related to infestation with *Schistosoma haematobium*. No eggs were found in any of the histological material in these 184 cases, but a devil's advocate might argue that they could have been missed, particularly in those 153 cases where only biopsies were available for examination. *Schistosoma haematobium*, however, does not occur in Uganda except in a small area in the Lango district in the central part of the country (Bradley and Davis, 1972). This series includes 3 cases of bladder cancer from this area, all of which were of transitional cell type. Infestation with *Schistosoma mansoni* is widespread but only light to moderate in severity. Owor (1971) found 67 cases of schistosomiasis in 7,200 autopsies in Kampala and in only 1 of these was there any bladder involvement. Anthony and MacAdam (1972) reviewed 30,700 biopsies and 3,369 autopsies from all Uganda for evidence of schistosomal infestation which was present in 122 cases, all but 2 of which involved the gastro-intestinal tract. Schistosomal bladder cancer is stated to have certain characteristics summarised recently by Makhyoun *et al.* (1971): it occurs in younger age-groups, in the sex predominantly engaged on working in the fields (males in Egypt and females in Portuguese East Africa) and spares the base of the bladder. The peak incidence in Uganda is in the middle and later years of life, males predominate in spite of the fact that females work in the fields and the base of the bladder is not conspicuously spared: 38% of bladder cancer where the site of the tumour was known arose from the trigone.

Table IV

Aetiological Factors in Carcinoma of the Urinary Tract

- Industrial carcinogens
  - 2 naphthylamine
  - 4 aminobiphenyl
  - benzidine
- Environmental factors
  - Smoking
  - *Schistosoma haematobium*
  - Diet (bananas, bracken fern, nitrosamines)
  - Tryptophan metabolites
  - Beta-glucuronidase
- Anatomical abnormalities
  - Exstrophy
  - Diverticula
  - Strictures

Diet may be an important aetiological factor in urinary cancer in Uganda. It has been suggested that carcinogens could appear in the urine as a result of a disturbed endogenous metabolism of tryptophan. This essential amino acid is either incorporated into the body proteins or is broken down to serotonin (5 hydroxytryptamine, 5HT), 5-hydroxyindoleacetic acid (5-HIAA) or nicotinic acid. There are several compounds along these metabolic pathways that are themselves, or that are converted to, carcinogenic orthoaminophenols, and these have been found in bladder cancer patients (Brown *et al.*, 1960). Steamed green bananas (matoke) are consumed in vast quantities by Ugandan Africans. Serotonin is known to exist in high concentration in bananas, and matoke-eaters have been shown to excrete abnormally large amounts of 5-HIAA in the urine (Crawford, 1962). Sorrentino (1961) produced bladder tumours in 16 of 22 guinea-pigs by feeding them a diet rich in bananas. Urinary excretion of 5-HIAA increased during the experiment. The possibility of other tryptophan derivatives being present in bananas also exists. Orthoaminophenols excreted in the urine are normally conjugated to form glucuronides or sulphates and are rendered harmless. Urinary beta-glucuronidase converts them back to free carcinogens. High levels of this enzyme have been found in a number of conditions that affect the bladder, but the data are complex and open to several interpretations (Kerr and Barkin, 1970). It is, however, at least possible that in Uganda a dietary overload with potential carcinogens exists and the effect of this is made manifest by stasis, infection and increased beta-glucuronidase activity due to urethral strictures.

A high incidence of urethral stricture in bladder cancer patients in Uganda has previously been reported from Jamaica by Weston (1961*a*) and Atkinson (1967) and from Uganda by Dodge (1964), who found it in 29 of 83 (35%) patients. The histological type of the tumour was squamous cell carcinoma in 33 (40%) of these patients but the relationship between presence of a stricture and type of tumour was not specified. He also commented on the unusually high incidence of urethral carcinomas. In this study a definite relationship has been established between presence of a stricture and squamous cell, but not transitional cell, carcinoma of both bladder and urethra. A similar relationship also appears to exist between strictures and adenocarcinoma. It is of interest to note that where non-tumorous bladder mucosa was available squamous and glandular metaplasia or carcinoma-in-situ were present in a high proportion of those with a stricture. These data suggest that urinary stasis enhances the development of carcinoma in the urinary tract and that it is also capable of modifying its histological type, probably through metaplasia. This enhancing effect is also reflected in the slight age difference that was found between those with and those without strictures. It may be further suggested that a similar mechanism operates in those areas where a high frequency of squamous cell carcinoma is linked with a high prevalence of urinary schistosomiasis.

The aetiology of these strictures is almost certainly gonococcal. Griffith (1963) reported an average attack rate of 15% per year for the adult male population of Uganda and also estimated that one-half of the women have been sterilised by gonorrhoea by the age of 30. He calculated the incidence rates of acute gonorrhoea and of urethral stricture in males in the various districts and obtained a significant inverse correlation with female fertility rates. Gonorrhoea is also very common in the West Indies, where it is locally referred to as "the gentleman's disease" (Weston, 1961*b*). Finally, this raises the possibility that urinary cancer in these areas may be due to a sexually transmissible, contagious agent. No studies have yet been carried out to explore this possibility, but it seems unlikely as exposure to such an agent should result in a more equal distribution of cancer in the two sexes.

Summary

Carcinoma of the urinary tract in Uganda shows some unusual features.

Squamous cell carcinoma is the predominant histological type. This is associated not with urinary schistosomiasis, which only occurs in one small area of the country, but with longstanding posterior urethral strictures of gonococcal origin. This association is found in both bladder and urethral carcinomas, the relative frequency of the latter being unusually high. Possible aetiological factors include dietary overload with tryptophan and increased beta-glucuronidase activity. The presence of a stricture is likely to have an enhancing effect on carcinogenesis and is the major factor in producing a high incidence of squamous cell growths through urinary stasis, infection and metaplasia.

My thanks are due to Dr A. C. Templeton who collected, organised and made available for study the material on which this report is based.

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Bilateral Breast Metastases from Carcinoma of the Prostate

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In patients with carcinoma of the prostate who develop breast tumours the differentiation between primary breast pathology and prostatic metastases is difficult to determine by conventional histological techniques. However, histochemical analysis of tumour tissue for its acid phosphatase content may provide the diagnosis, as illustrated in the following case.

Case Report

A 75-year-old male presented in October 1970 with a 3-month history of anorexia and urinary frequency. There were no associated symptoms and no relevant past history. On examination the only significant findings were that he was clinically anaemic, had a firm non-tender fixed mass in the left supraclavicular fossa, and an enlarged irregular prostate with obliteration of the median sulcus.

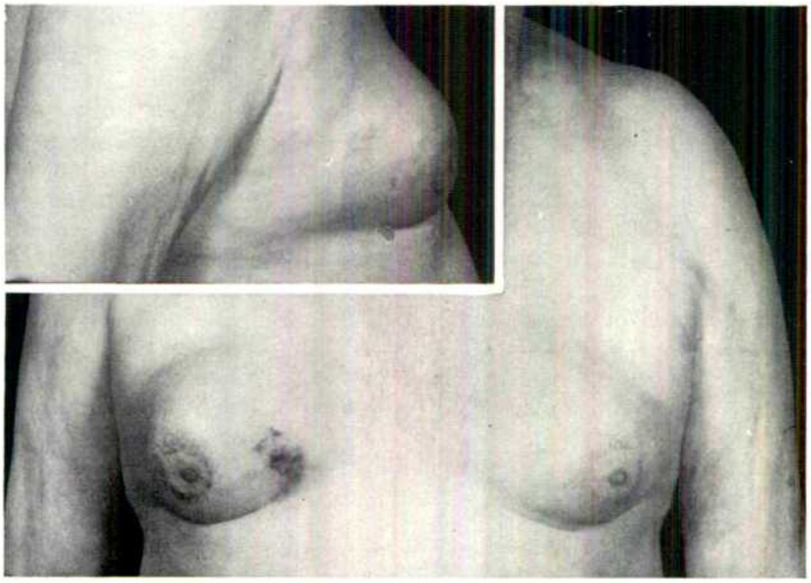

Fig. 1. Shows bilateral breast enlargement. There is some bruising of the right breast at the biopsy site.

Laboratory investigations: Haemoglobin, 6·5 g per 100 ml; E.S.R. 160 mm in the first hour; a blood film showed an early leucoerythroblastic picture; urea, 33 mg per 100 ml; serum acid phosphatase 260 units. I.V.P. showed a mild bilateral hydronephrosis and a moderate residual volume of urine after micturition. Radiography showed several sclerotic deposits in the lumbar spine and pelvis. Biopsy of the supraclavicular mass revealed fatty connective tissue widely infiltrated with anaplastic spheroidal cells compatible with a diagnosis of prostatic metastasis. After a blood transfusion of 6 units he was started on fosfestrol (Honvan) 1,000 mg intravenously, daily for 7 days followed by 250 mg orally, b.d. One month later he was well, with less urinary frequency. His serum acid phosphatase had fallen to 42·5 units. Three months later, however, he had developed diarrhoea and had stopped taking the Honvan. He was therefore started on stilboestrol 5 mg t.d.s. and apart from minor joint pains felt well. 18 months later, in May 1972, he was noted to have bilateral painless breast enlargement. The right breast contained a firm, round mass which was fixed to the skin with some inversion of the nipple. The left breast contained a smaller mass with no discrete borders (Fig. 1).

Biopsy of the right breast lesion showed this to be a poorly differentiated spheroidal cell carcinoma. In June 1972 he had a right simple mastectomy and an excision biopsy of the lesion in the left breast. Histological examination showed a tumour similar to that of the biopsy from the right breast and histochemical analysis gave a positive acid-phosphatase reaction, suggesting very strongly that these tumours were prostatic metastases. His oestrogen therapy was therefore continued and in August 1972 he had a bilateral subcapsular orchidectomy. During this admission to hospital he was given a 3-unit blood transfusion as haematological investigations revealed a haemoglobin of 9·8 g % with a blood film showing a leucoerythroblastic picture similar to previous examinations. He made an uneventful postoperative recovery and is well and active with no specific symptoms 4 months later (December 1972).

Comment

General Discussion. The development of a breast lesion in a patient with carcinoma of the prostate receiving oestrogen therapy is rare. There are only 18 such cases reported in the English literature: 16 reviewed by Lome and Austen (1970), and 1 each reported by O'Grady and McDivitt (1969) and Hartley and Little (1971). Of these, the reported histological interpretation was metastatic in 9 cases, primary in 6 cases and in the remaining 3 cases no histological interpretation was offered. But, as already stated, the only reliable differentiating guide is obtained by selective staining for acid phosphatase and in only 4 of the previously recorded cases was this test performed. In each case where the acid phosphatase reaction was recorded it was reported as positive and the breast lesion therefore deemed metastatic. Campbell and Cummins (1951) were the first to report the acid phosphatase reaction of 1 such tumour and to indicate that an element of doubt must remain over the correct diagnosis in the reported cases, which now number 14, where histochemical analysis was not performed. The interpretation of the pathology in the first few recorded cases was strongly affected by the belief that oestrogen therapy could be an aetiological factor in the development of carcinoma in the male breast. Lacassagne had in 1932 induced breast tumours in male mice by the administration of oestrogens. However, there is now considerable evidence that this is not a significant factor in the aetiology of human male tumours. In a series of 198 cases of primary carcinoma of the male breast reviewed by Holleb, Freeman and Farrow (1968) no cases were associated with concomitant oestrogen therapy. They also quoted a review made in 1946 of more than 17,000 cases of prostatic carcinoma treated with oestrogens which yielded only 2 cases of breast cancer. Amongst their conclusions were "at present there does not appear to be any causal relationship between male breast cancer and oestrogen administration". More recently this observation has been confirmed by Crichlow (1972) in a review of the world literature on carcinoma of the male breast. It is of interest that in those cases previously recorded which were deemed metastatic by histological methods, where survival after the development of breast metastases was recorded, the average survival was only 4 months.

Pathological Discussion. In 1935 Kutscher and Wolbergs identified a phosphatase in urine with optimum activity at pH 4-5 and showed that it was derived from prostatic tissue. Gomori (1941) devised a histochemical test for acid phosphatase using lead sulphide as an indicator, after fixation in ice-cold acetone and paraffin embedding. Maximum activity was present in normal and malignant prostatic tissue, but acid phosphatase could be detected in normal and neoplastic conditions of the gastrointestinal tract, though breast was negative as was pancreas and ovary. Gomori's original method was somewhat capricious, but was made more reliable by the modification of Wolf, Kabat and Newman (1943). Abdul-Fadl and King (1947, 1948), anxious to differentiate the prostatic acid phosphatase in serum from that in erythrocytes, showed that the former was inhibited by tartrate, whereas the acid phosphatases of erythrocytes and most other tissues was inhibited by formalin, which had no effect on prostatic phosphatase. It was at this time that Dean and Woodward (1947) showed that it was possible to distinguish prostatic carcinomatous tissues from neoplastic tissues in adjoining areas of rectum and bladder by estimating the acid phosphatase content of tumour extracts.

As has been mentioned, Campbell and Cummins (1951) were the first to use the histochemical acid phosphatase technique to determine whether or not mammary tumours developing during oestrogenic therapy for prostatic carcinoma were metastases from the prostate or hormonally induced primary mammary tumours. The neoplastic tissue of the breast and prostate from the postmorten examination of their case both gave a strong positive reaction for acid phosphatase. Glück (1952) was unconvinced by Campbell and Cummins' histochemical findings and obtained positive acid phosphatase reactions in over 70% of a large number of biopsies of normal, hyperplastic and neoplastic breast tissue using their technique.

Histochemists were dissatisfied with the Gomori method and its modifications for acid phosphatase. Reiner, Rutenburg and Seligman (1957), in a review of acid phosphatase activity in human tumours, used an azocoupling method which they had developed in which biopsies were fixed in cold neutral 10% formalin for 24 hours and then frozen sections were cut on which the reaction was applied; they obtained a strong positive reaction in prostatic carcinoma and gastro-intestinal neoplasms and moderate reactions in neoplasms of the breast, thyroid and skin. They noted that fixation in acid formalin reduced the enzyme reaction but reported a case in which a lymph node, infiltrated with a poorly differentiated carcinoma, gave a strong positive reaction for acid phosphatase although the material had been fixed in non-buffered formalin for 2 days and surgical investigations confirmed that the primary growth was in the prostate.

Fanger and Barker (1959), in a detailed histochemical study of breast tissues, obtained positive acid phosphatase reactions in a range of pathological conditions using both the azo and lead methods on frozen sections after fixation in neutral formalin for 2 hours.

Zugibe (1970) was the first histochemist to recognise the problem of determining whether an undifferentiated carcinomatous metastasis was of prostatic origin or not, and applied the inhibition technique devised by Abdul-Fadl and King (1948). Zugibe recommends that unfixed frozen sections should be stained by the azocoupling method, which would be controlled by adding formalin or tartrate to the substrate and control sections of prostate and non-prostatic tissue should be stained at the same time. The addition of tartrate will inhibit the reaction with prostatic acid phosphatase whereas the addition of formalin inhibits the acid phosphatase of tissue other than prostate.

Of the 4 cases already reported of breast metastases from prostatic carcinoma in which a histochemical test was applied, Campbell *et al.* (1951, 1962) merely state that the Wolf, Kabat and Newman method was used, so presumably the material was fixed in acetone, though in their second case they estimated the acidoglycophosphate content of the breast. Boutouras, Woodhams and Brown (1965) explain that the prostatic origin of the breast neoplasm "was confirmed by physico-chemical acid phosphatase test" while Lome and Austen (1970) found that "the Gomori acid phosphatase stains gave positive results".

Histochemical Investigations in this Case

In the case reported here, the material consisted of a formalin fixed paraffin block, and the remains of the surgical specimen which had been preserved in formal saline (pH 4·8) at room temperature for 4 weeks and so had not received the special care which the histochemist requires.

However, haematoxylin eosin stained sections of the breast showed a diffuse infiltration with a spheroidal cell carcinoma and normal mammary ducts could be seen lying in the carcinomatous tissue (Fig. 2); it would be difficult on morphological grounds to state categorically that the tumour was not a poorly differentiated primary carcinoma of the breast and stains for mucins gave no help.

Cryostat sections of the formalin-fixed material were stained for acid phosphatase using the azocoupling method of Rosales *et al.* (1966). The tumour tissue stained very strongly, as did control sections of prostatic hyperplasia which had been fixed in formalin at pH 7·0 for 7 days. The addition of 10% 0·2M tartrate solution to the incubation medium markedly reduced the staining of the tumour tissue from the breast and the prostatic control.

However, in view of the reports by Glück (1952) and Fanger and Barker (1959) that primary breast carcinomata gave strong acid phosphatase reaction using their technique, it seemed desirable to test this, using material which had received similar treatment to the breast specimen of the case reported here. Accordingly 4 specimens of primary breast carcinomata which had been fixed in formalin at pH 7·0, 1 for 24 hours, the others for 7 days, were treated in a similar manner and all failed to stain, although the prostatic controls stained strongly.

Six further breast specimens (4 carcinomata and 1 fibro-adenosis of the female breast and 1 primary carcinoma of the male breast) were obtained in the unfixed state. Cryostat sections were prepared and all gave a strong positive reaction for acid phosphatase; post-fixation in formalin (pH 7·0 for ½ hour) reduced the staining slightly, the reduction was more marked after 1 hour and there was no staining after 3 hours, although post-formalin fixation had no effect on the control prostatic tissue. Addition of tartrate to the incubation medium inhibited the staining of the breast carcinomata and reduced the staining of the prostatic control.

Numerous other experiments were carried out, which will be reported elsewhere, but it is possible to conclude that if carcinomatous tissue which has been fixed in formal saline for more than 24 hours gives a positive acid phosphatase reaction with an azocoupling technique, it is highly probable that it is of prostatic origin and this probability is increased if addition of tartrate to the incubation medium inhibits the reaction; naturally it is necessary to have control tissues treated in a similar way. On the other hand, if fresh unfixed tissue or tissue fixed in acetone should give a positive acid phosphate reaction it cannot be presumed to be of prostatic origin, unless the reaction is not inhibited when formalin is added to the substrate and is inhibited by the addition of tartrate (Fig. 3).

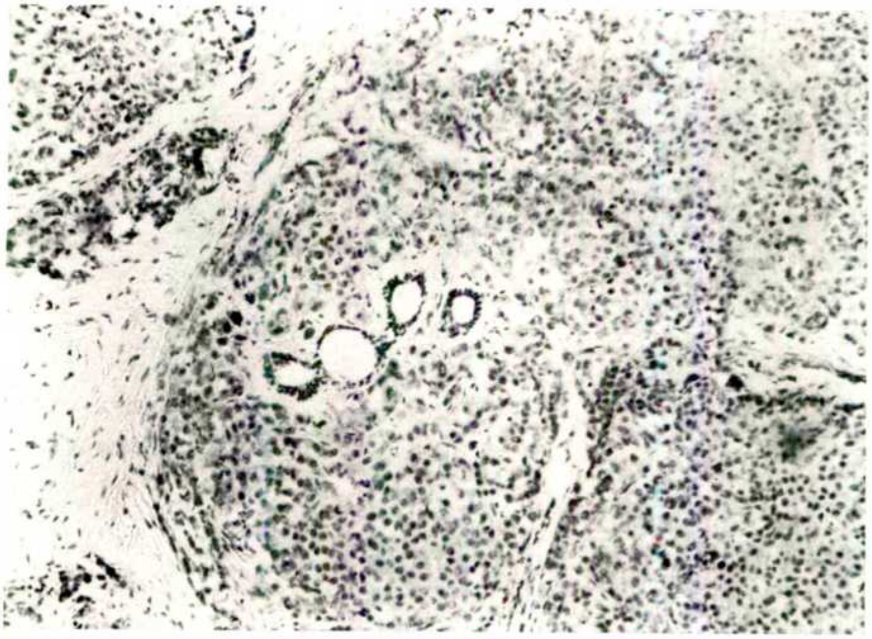

Fig. 2. Section of breast tumour of patient (Haematoxylin-eosin ×65). There is a diffuse infiltration with a poorly differentiated spheroid cell carcinoma which is surrounding the normal breast ducts.

By adopting these procedures it should usually be possible to determine whether or not a breast tumour is of prostatic origin so that treatment may be adjusted accordingly.

Summary

A case of bilateral breast metastases developing in a patient with carcinoma of the prostate while on oestrogen therapy is described.

Differentiation between prostatic metastases and primary breast tumours under these circumstances is important as the treatment for each is different.

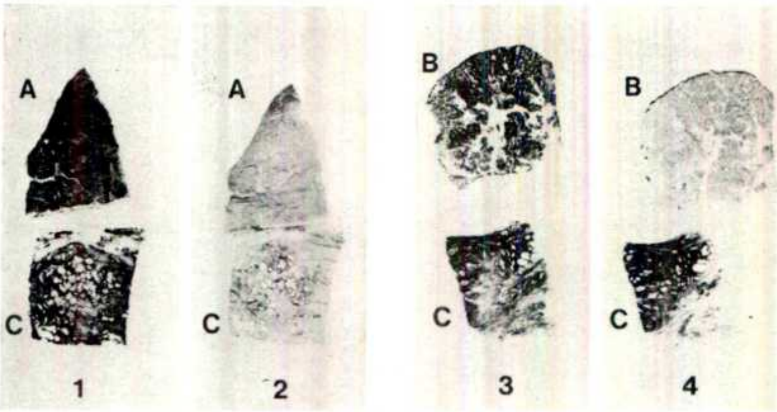

Fig. 3. Acid phosphatase reactions. A, Section of breast tumour of patient. B, Section of primary carcinoma of breast. C, Section of normal prostate.

1 Acid phosphatase reaction on formalin fixed material.
2 Acid phosphatase reaction on formalin fixed material after addition of tartrate to substrate.
3 Acid phosphatase reaction on fresh unfixed material.
4 Acid phosphatase reaction on fresh unfixed material after addition of formalin to the substrate.

It can be seen that formalin fixation does not inhibit the phosphatase reaction on the patient's tumour or the prostatic control (1), although the reaction on both the tumour and prostatic control is inhibited by the addition of tartrate (2). On the other hand, fresh unfixed primary carcinoma of the breast gives a strong acid phosphate reaction as does the prostatic control (3) but the addition of formalin to the substrate inhibits the reaction on the primary breast carcinoma but has no effect on the prostatic control (4).

Such differentiation may be difficult by conventional histological techniques, but histochemical analysis can resolve the problem, as was possible in this case.

We would like to thank Mr E. J. C. Wynne, M.A., M.Chir., F.R.C.S., for permission to report this case and for his help and advice.

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Some Observations on the Quantitative Analysis of over 1000 Urinary Calculi

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For 4 years a system of stone analysis based on the quantitation of 5, and subsequently 6, of the most frequent parameters was in operation in the author's laboratory. By this system, described by Westbury and Omenogor (1970), 1,022 stones were investigated. From the results a study was made of the differences in the chemical aspect of stone formation between:

(*a*) Male and female patients.
(*b*) Patients of the same sex from various ethnic groups. As overseas male patients were far more numerous, females were excluded from this study.
(*c*) Adults and children.
(*d*) Patients suffering from various conditions of which repeated stone formation is a distinguishing clinical feature, *i.e.* hyperparathyroidism, sponge kidney and idiopathic hypercalciuria.
(*e*) Staghorn calculi as opposed to those of more regular or indeterminate shape.
(*f*) Stones above and below 100 mg in weight.

A further study was made into the degree to which persistent stone formers (those producing more than 1 stone in the 4-year period) were able to repeat the pattern of chemical composition in later stones.

Materials and Method

The system of analysis as originally conceived has already been described (Westbury and Omenogor, 1970). A brief summary is given below including recent modifications.

Pretreatment

On reception in the laboratory each stone specimen was documented, and its shape and colour noted. In the case of very large stones, an apparently representative portion was selected for analysis. The calculus was freed from extraneous matter (blood, tissue, etc.), dried, weighed and pulverised with pestle and mortar. If the specimen consisted of many discrete calculi, one only was selected at random for analysis.

Preparation of Aliquots

Two 10-mg aliquots of homogenous stone powder were weighed. One of these was dissolved in 5 drops of concentrated hydrochloric acid with the application of heat. On cooling, the solution was transferred to a 25-ml volumetric flask and the contents made up to the mark with deionised water.

The second aliquot was dissolved in 2 ml of a decalcifying solution consisting of 5% (w/v) ethylene diamine tetra-acetic acid (A.R. recrystallised) adjusted to pH 7·8 with sodium hydroxide. When solution was complete, which sometimes entailed leaving overnight, the final volume was made up to 10 ml.

Treatment of Stones weighing less than 20 mg

Very small specimens presented a 2-fold problem. Not only was the stone often too small for the routine procedure, it was also difficult to recover sufficient powder from the mortar after pulverisation. In these cases the second aliquot was omitted, and after the transfer of a minimal amount of powder to spot-trays for qualitative tests, the whole of the remaining stone material was weighed and dissolved in acid.

Table I

Summary of Methods

Estimation	Aliquot Used	Method	Reference
Calcium	Acid	Flame photometry Zeiss PMQII	Westbury and Omenogor (1970)
Oxalate	Acid	Permanganate titration	Archer, Dormer, Scowen* and Watts (1957)
Phosphorus	Acid	Auto-analyser II	Technicon Methodology
Magnesium	Acid	Atomic-absorption Perkin Elmer 290	Dawson and Heaton (1961)
Ammonium	Acid	Nesslerisation	Westbury and Omenogor (1970)
Uric Acid	E.D.T.A.	Auto-analyser II	Technicon Methodology

* This describes a method for urinary oxalate. It is used for calculi, omitting the pre-treatment stage.

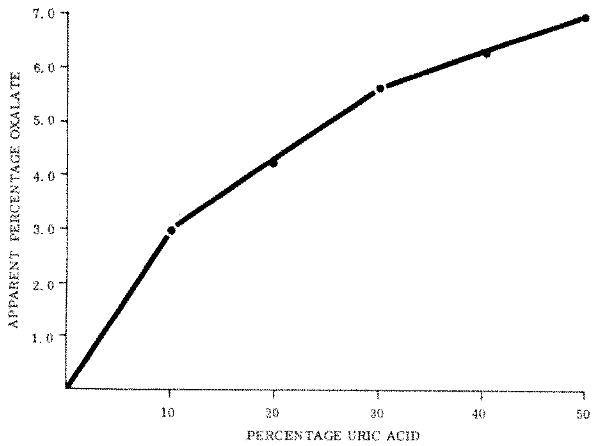

Fig. 1. Correction chart for apparent oxalate in uric acid stones.

Analysis of Quantitated Parameters

The aliquots were introduced into the normal laboratory work-load. The acid aliquot was used for calcium, oxalate, phosphorus, magnesium and ammonium contents; the E.D.T.A. aliquot for uric acid alone. The methods of estimation were accordingly for the most part incidental in that it was desired to assimilate the analysis of calculi as completely as possible into laboratory routine. The methods currently in use are shown in Table I.

The estimation of oxalate posed a problem, in that the uric acid also reduced potassium permanganate. This was solved satisfactorily by assessing the "oxalate equivalent" of serial dilutions of uric acid. The correction curve is shown in Figure 1.

Unquantitated Parameters

A small amount of stone powder was transferred to two spot-trays for tests for carbonate and cystine. To the first, two drops of concentrated hydrochloric acid were added. Effervescence indicated the presence of carbonate.

On the second spot-tray the nitroprusside reaction for cystine was carried out. The reagents added were a drop of 5% potassium cyanide followed after a 5-minute interval by one of fresh 5% sodium nitroprusside. An unequivocal magenta colour denoted the presence of cystine.

In practice, a third spot-test for uric acid was found advisable using the cyanide solution mentioned above and Folin's uric acid reagent (obtained commercially). This was necessary for testing small stones, but it also detected those calculi in which a high percentage of uric acid necessitated dilution before auto-analysis.

Results

From 28.2.68 to 28.1.72, 1,033 alleged urinary calculi and accretions were successfully analysed. These could be classified primarily as follows:

Genuine calculi from human patients	1,022
Genuine calculi from experimental animals	6
Artefacts and hoaxes	5
	1,033

The results of the 1,022 analyses from human patients were further categorised:

(*a*) By parameters. Histograms (Figs. 2 to 7) were prepared showing the frequency distributions of varying contents of calcium, oxalate, phosphorus, magnesium and other constituents.

(*b*) By groups of patients. Differential assessments were made of the stones from the following sources:

(i) Female patients (212 stones). These were not subdivided because few of them came from overseas.
(ii) Western European male patients (533 stones).
(iii) Eastern European male patients (37 stones).
(iv) Afro-Asian male patients (147 stones).

The principal criteria in allotting a patient to categories (ii), (iii) and (iv) were the patient's surname and address. The largest group of Eastern Europeans were ostensibly Greek (18) and most of the rest had Slav surnames. The choice of the title Afro-Asian for category (iv) was made principally to justify the inclusion of a small group from India (10); the bulk of this category were Arabs. The sometimes limited information of addressographed labels suggested that most of the Islamic world, including Turkey, was represented.

(v) Children (36 stones).

The criterion of occupancy of a bed in the children's ward.

(vi) Patients suffering from hyperparathyroidism (23 stones).
(vii) Patients suffering from sponge kidney (16 stones).
(viii) Patients suffering from idiopathic hypercalciuria (46 stones).

The sample sizes in these classes were disappointing, because, in many cases, the stones relating to known cases of hyperparathyroidism, sponge kidney and idiopathic hypercalciuria were presented before the present methods of analysis were instituted. There is also a time lag between the initial diagnosis of urolithiasis and a more precise differential diagnosis.

(*c*) By stone morphology. The most clear-cut distinction was that betweeen the characteristic lateral branching shape of the fragile "staghorn" and the more usual hard spherical nature of the bulk of the specimens. The results from 62 unequivocal staghorn calculi were examined.

(*d*) By size. For this purpose an arbitrary dividing line was drawn at 100 mg. As this part of the study was an afterthought, this information is not included in the histograms. 270 of the stones were under 100 mg in weight.

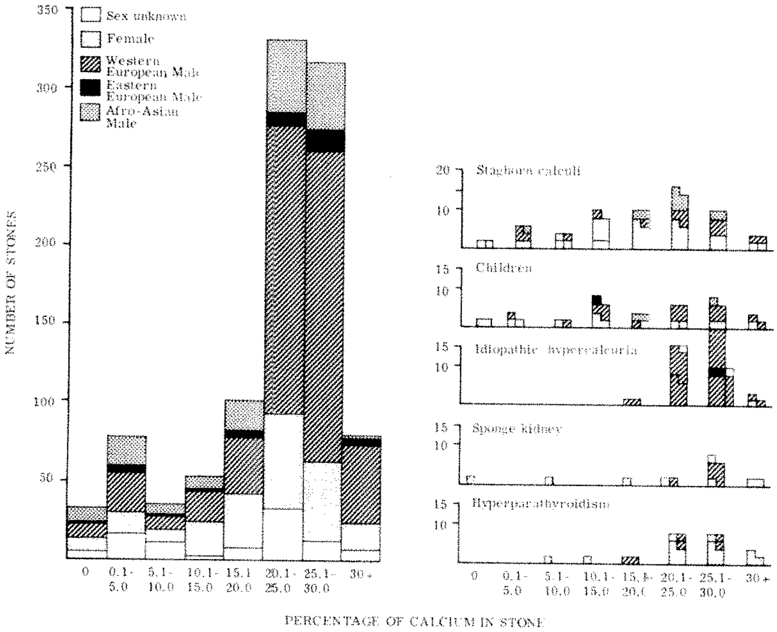

Fig. 2. Histogram of calcium percentage frequency in individual stones

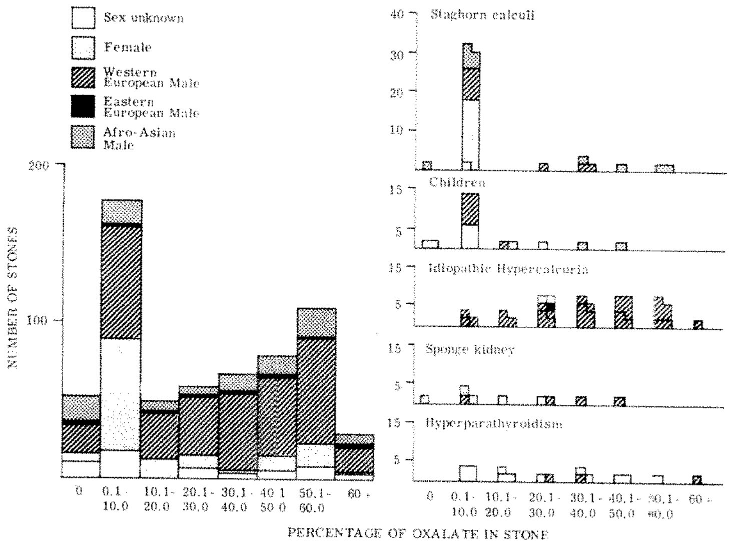

Fig. 3. Histogram of oxalate percentage frequency in individual stones.

A separate investigation concerned the ability of recurrent stone formers to repeat the relative chemical composition of the first stone in later specimens. Specimens from patients producing more than 1 stone in the 4-year period were included. There were 2 series of 5 stones each, 3 of 4, 8 triplets and 43 pairs of primarily calcium-containing stones. Excluded were 8 pairs of cystine stones and 1 collection of 6 stones consisting almost entirely of uric acid.

It was assumed that the first stone to be received was the initial stone of the series, and percentage composition for each parameter in later stones was plotted against initial percentage. It was noted that patients with a known history of recurrent urinary infection presented a more varied picture than patients without such a history. For this reason a distinction was made between "sterile" and "infected" calculi. The coefficients of correlation obtained are shown in Table VII.

In addition to the histograms, the results are further summarised in Table II which shows the mean percentage composition of the stones in each group or type, and Table III, which shows likewise the percentage of positive findings. As Poisson-type distributions are markedly absent in the histograms, an attempt was made to assess the significance of the differences between groups by applying the χ^2 test. For each of the smaller groups the distribution of stones between the various concentration ranges of the parameter was compared with a numerically equal aliquot of the total sample or the larger group. In the case of the qualitative parameters, these concentration ranges were simply absence or presence of carbonate and cystine respectively. The values of χ^2 obtained were referred to probability tables. These results are shown in Table IV.

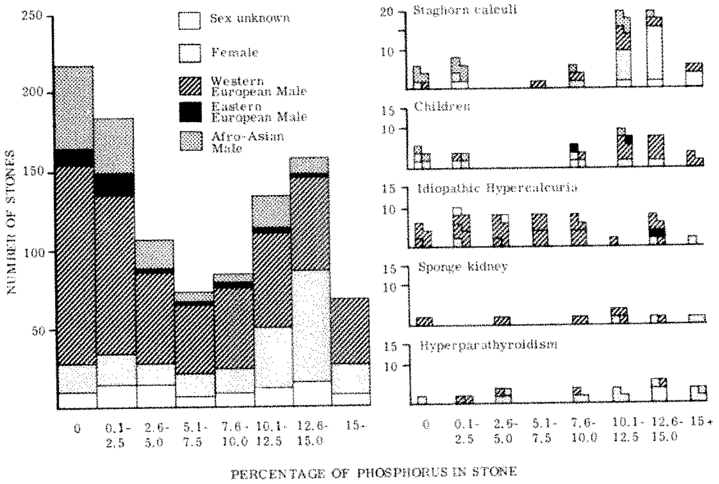

Fig. 4. Histogram of phosphorus percentage frequency in individual stones.

Discussion

The scheme described for stone analysis is simple, rapid and fits neatly into hospital laboratory routine, but it has one great disadvantage. Except for pure cystine stones, it gives scant information as to the molecular nature of the accretion. For this purpose crystallographic or other specialised physical methods are necessary, and Herring in a classic study (1962) has shown how many different chemical substances may be found in 10,000 stones. Notwithstanding the attempt of Hodgkinson, Peacock and Nicholson (1969) to assess from the principal elemental parameters the proportions of calcium oxalate, apatite and magnesium ammonium phosphate present in a given stone, the variety of constituents renders this undertaking beyond the scope of purely chemical analysis.

But a minute crystallographic description is not relevant to the clinician, and a possible way out of this difficulty is to observe how well the stone composition fits into certain fairly well defined patterns. An attempt at such a scheme of identification is shown in Table V.

Figure 8 is a histogram showing the breakdown of 1,022 calculi in this study on such an empirical basis. No mathematical treatment of this material has been made because of the subjective nature of the interpretation. Table VI shows the histogram information in terms of the percentage of each type in each category of stone former.

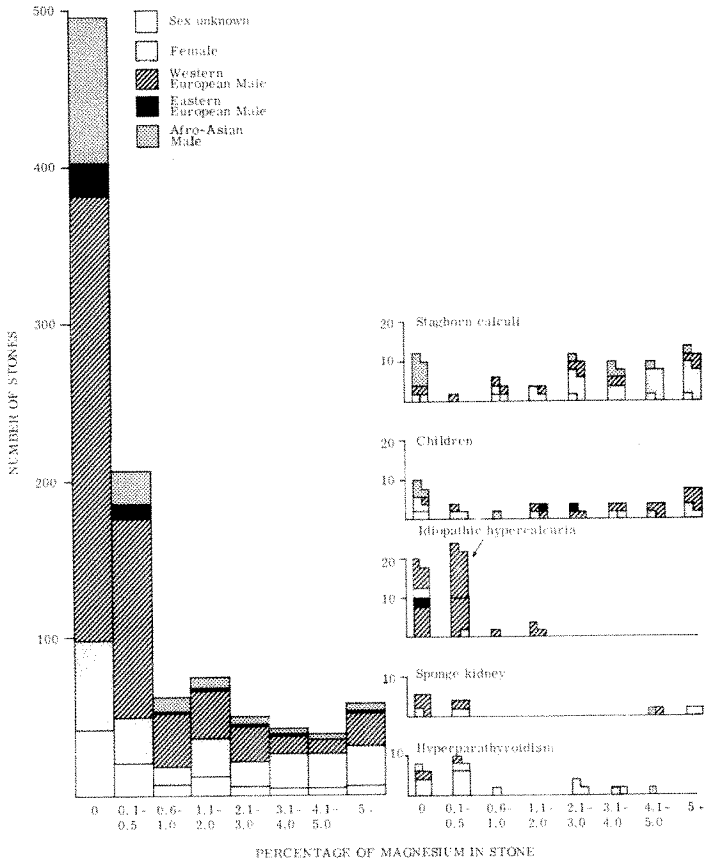

Fig. 5. Histogram of magnesium percentage frequency in individual stones.

From the various strands of statistical evidence, relationships between stone and stone-former in 6 areas of investigation began to emerge:

1. *Sex*

The most significant and explicable difference is that between male and female patients. This relates to the greater risk of urinary infection incurred by women. The correlation between recurrent urinary infection and chemical composition of stones has been investigated in the earlier work of Westbury and Omenogor (1970). Thus Figures 2 to 8, and Tables II, III and VI show that the typical "male" stone is composed mainly of calcium oxalate, and that the typical "female" stone conforms to the triple phosphate or carbonate-apatite pattern, frequently staghorn in appearance.

2. *Environmental Factors*

The most striking difference between ethnic groups of stone formers is in the proportion of uric acid stones. Since hyperuricaemia is predominantly a male trait, these stones are almost invariably produced by men, but, as Table VI shows, the proportion of such stones in the pure state is twice as great in the Eastern groups. Stones from Afro-Asian males also contain significantly less calcium and phosphorus than Western European males, and the same trend would seem to be present in the Eastern European group.

The significance of these findings is far from clear. The studies of various workers suggest that the environmental factors in the aetiology of urolithiasis are complex. In this context the series of studies conducted on a geographical basis by Lonsdale, Sutor and Wooley and continued by Sutor and Wooley (1968, 1971) provide much material for speculation. The roles of climate (Frank and De Vries, 1966), of diet (Anderson, 1962), and of the patients' working conditions (Blacklock, 1965) have been investigated.

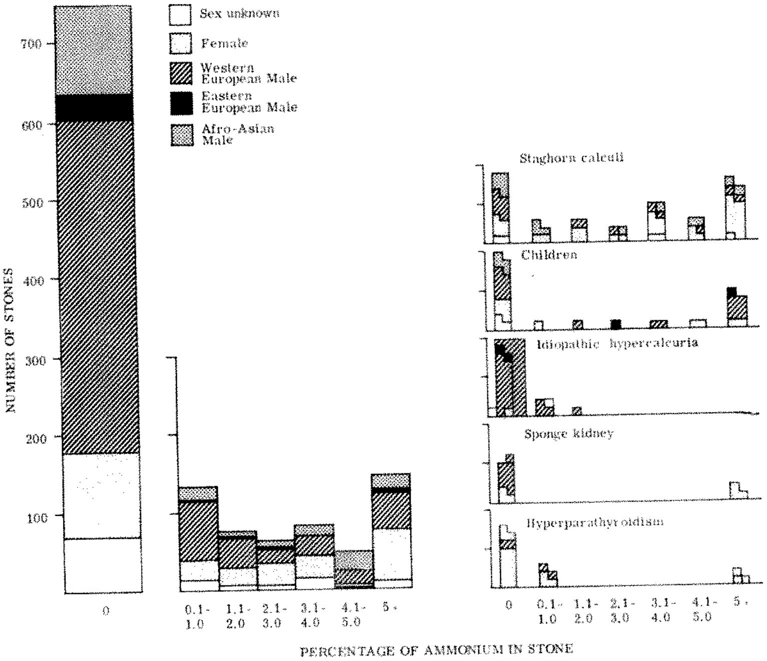

Fig. 6. Histogram of ammonium percentage frequency in individual stones.

3. *Age*

Children's stones contain less calcium and oxalate, and more phosphorus and magnesium than the typical stone of the whole group (Table II, Figs. 2 to 5). Although the collection of stones from little girls has perhaps been distorted by the presence of 6 cystine specimens, it is interesting that the composition of children's stones generally, and those of little boys especially, bears a general resemblance to those of adult females. The relationship would appear to be that children are more likely to have an associated urinary infection, which alters the composition of the urine in such a way as to favour the production of proliferative calculi.

4. *Diagnostic Considerations*

Despite the small number of stones from patients whose medical histories were readily available and sufficiently extensive, significant findings were made concerning calculi in idiopathic hypercalciuria (Tables II to IV, Figs. 2 to 6). These patients' stones contain much more oxalate than sponge kidney stones, and probably more oxalate than those produced in hyperparathyroidism; they contain less phosphate than hyperparathyroid stones and less magnesium than stones in either of the other two groups. They are also almost always devoid of carbonate.

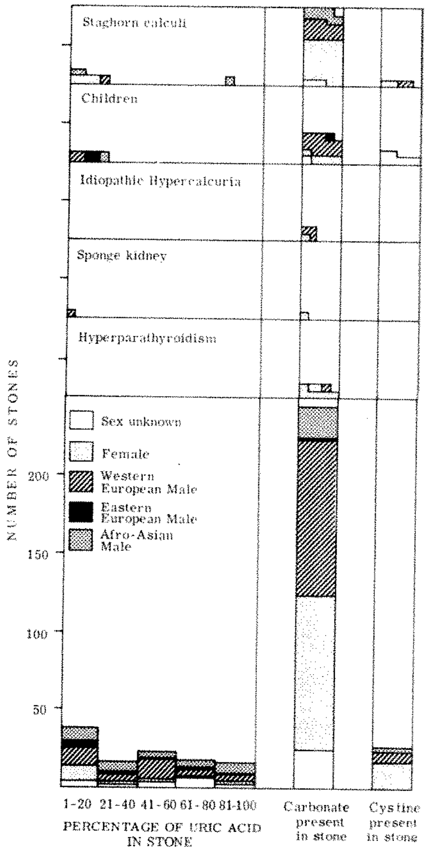

Fig. 7. Histogram of frequency of other constituents (positive findings only).

These groups are not, however, strictly comparable in that nearly all the hyperparathyroid patients were female and nearly all the idiopathic hypercalciurics were male. For this reason the comparison of greatest value is that between the latter group and cases of sponge kidney, in which the proportion of each sex is approximately the same. A deduction from the figures, necessarily tentative in view of the small numbers, would be that there is in idiopathic hypercalciuria a pattern of mineral excretion which favours the deposition of oxalate, but inhibits the production of triple phosphate and apatite calculi. When idiopathic hypercalciurics do form stones of mixed phosphate/oxalate composition, these conform to the "sterile" pattern as illustrated in Table VI.

It was also observed that nearly half of the stones from cases diagnosed as idiopathic hypercalciuria weighed less than 100 mg. However, an attempt to show that the oxalate content was higher in the smaller stones was unsuccessful.

The observation by Chambers, Hodgkinson and Hornung (1972) that stones formed in primary hyperparathyroidism tend to be composed of calcium phosphate received some support in this study, but with qualification. The much higher proportion (75%) found in their investigation was, in fact, 3 out of only 4 specimens. It is clear that many more specimens need to be analysed and much more clinical information needs to be accumulated before the significance of these findings can be assessed.

Table II

Mean Percentage Composition of Types of Calculus

Description or Source of Stone	Sex of Patients	Number of Stones	Calcium	Oxalate	Phosphorus	Magnesium	Ammonium	Uric Acid
Total sample	212 Female 717 Male 95 Sex unknown	1,022	21·50	28·47	6·62	1·10	1·02	4·79
From adults	Female	196	20·74	17·59	9·59	2·13	2·10	1·07
From adults	Male	694	22·33	31·35	5·71	0·67	0·63	5·19
From Western Europeans	Male	533	23·34	30·08	6·60	0·85	0·66	2·74
From Eastern Europeans	Male	37	20·06	31·74	4·62	0·59	0·38	12·04
From Afro-Asian	Male	147	19·02	32·57	3·28	0·68	0·91	11·11
In hyperparathyroidism	19 Female 4 Male	23	25·00	26·13	9·88	1·04	0·46	0
In sponge kidney	5 Female 9 Male	14	24·14	18·56	9·27	1·90	0	0·19
In idiopathic hypercalciuria	1 Female 45 Male	46	26·47	37·41	6·28	0·22	0·03	0
From children	Female	16	12·50	4·83	6·17	1·91	2·06	0
From children	Male	23	18·87	11·97	11·01	3·81	3·23	1·40
Staghorn	Female	33	16·46	3·91	11·70	4·05	4·46	0·18
Staghorn	Male	29	20·11	17·04	8·72	2·41	2·31	3·78
Less than 100 mg	Female	36	22·45	26·92	8·65	1·12	1·60	0·34
Less than 100 mg	Male	234	22·73	35·61	4·70	0·40	0·27	6·65

Table III

Percentage of Positive Findings in Types of Calculus

Description or Source of Stone	Sex of Patients	Calcium	Oxalate	Phosphorus	Magnesium	Ammonium	Uric Acid	Carbonate	Cystine
Total sample	212 Female 717 Male 95 Sex unknown	97·4	91·8	78·6	51·2	27·1	10·1	24·5	2·5
From adults	Female	98·0	96·6	95·4	76·0	45·9	4·6	44·4	4·6
From adults	Male	97·4	91·7	72·3	45·4	21·3	10·8	17·6	1·4
From Western Europeans	Male	98·3	96·6	75·6	47·4	20·4	5·4	17·9	1·3
From Eastern Europeans	Male	97·3	90·0	76·0	46·0	13·5	29·8	5·4	0
From Afro-Asians	Male	94·5	89·8	65·9	35·9	24·5	21·7	15·0	2·0
In hyperparathyroidism	19 Female 4 Male	100·0	100·0	95·7	70·0	17·4	0	26·0	0
In sponge kidney	5 Female 9 Male	95·7	88·9	85·7	57·5	0	7·2	7·1	0
In idiopathic hypercalciuria	1 Female 45 Male	100·0	100·0	89·2	58·8	4·4	0	0	0
From children	Female	81·3	85·7	62·5	50·0	37·5	0	31·3	37·5
From children	Male	100·0	100·0	91·3	82·6	65·2	17·3	60·9	0
Staghorn	Female	93·9	100·0	93·9	93·9	87·9	3·0	90·9	6·1
Staghorn	Male	100·0	94·7	86·2	69·0	65·5	6·9	58·6	6·9
Less than 100 mg	Female	97·2	95·5	77·8	63·9	30·6	5·6	27·8	2·8
Less than 100 mg	Male	97·4	91·1	73·5	32·9	15·8	12·0	6·4	0·4

5. *Size and Shape of Stone*

In view of the accepted view (Lonsdale, Sutor and Wooley, 1968) that the majority of large stones consist of an oxalate core surrounded by phosphate at the periphery, it is not surprising that the smaller stones contained significantly more oxalate and less phosphate (Table II). The demarcation was, however, not as clear-cut as was expected, and it is an oversimplification to make a hard and fast division between small "hypercalciuria" stones, consisting of phosphate aggregations. Yet the notion of a hard oxalate core, often so small that it cannot be detected chemically,

Table IV

Statistical Evaluation

Comparison between		χ^2 Values							
Estimated Distribution of Aliquot of	Observed Distribution in	Calcium	Oxalate	Phosphorus	Magnesium	Ammonium	Uric Acid	Carbonate	Cystine
Total sample	Stones from female patients	34·1*	56·6*	29·6*	88·7*	286·7*	68·3*	195·8*	8·4*
	Stones from male patients	13·4	9·3	29·6*	24·8*	29·8*	1·7	2·2	0·5
	Stones from W. European males	30·1*	15·1	9·4	22·5*	22·5*	36·6*	17·8*	5·8*
	Stones from E. European males	7·4	8·5	13·4	3·4	5·8	6·1	5·4	1·1
	Stones from Afro-Asian males	12·4	18·6*	32·9*	14·0	2·1	12·9*	7·6*	0·2
	Stones in hyperparathyroidism	6·0	10·2	42·1*	26·3*	9·2	2·2	0·2	0·6
	Stones in sponge kidney	17·0	4·3	15·5	33·2*	4·2	2·6	1·3	0·4
	Stones in idiopathic hypercalciuria	13·8	22·8*	18·1*	24·7*	11·0*	4·3	10·0*	1·0
Adult stones	Children's stones	45·0*	15·3*	15·4*	19·1*	13·4*	12·7*	7·2*	16·0*
Total sample	Staghorn calculi	34·5*	50·0*	41·8*	128·5*	59·2*	3·7	21·2*	0·3
Stones over 100 mg	Stones under 100 mg	24·0*	70·8*	40·7*	63·2*	58·7*	7·8	30·1*	3·0
Stones from male patients	Stones from female patients	56·0*	117·5*	160·5*	154·4*	63·8*	13·8*	102·3*	10·0*
Stones from W. European males	Stones from E. European males	4·8	8·6	11·8	1·6	6·8	1·0	3·0	...
Stones from W. European males	Stones from Afro-Asian males	50·2*	32·9*	80·2*	17·7	3·5	22·7*	1·2	0·9
Stones in idiopathic hypercalciuria	Stones in sponge kidney	50·2*	17·5*	9·9	5·8	...	...	...	...
Stones in idiopathic hypercalciuria	Stones in hyperparathyroidism	4·7	12·8*	14·0*	15·2*	6·3	...	...	...

* Statistically significant ($P < 0·05$).

Table V

Examples of Typical Stone Patterns—Percentage Composition

Type	Calcium	Phosphorus	Magnesium	Uric Acid	Ammonium	Oxalate	Carbonate	Cystine	Remarks
"Pure" oxalate	29·2	1·6	Nil	Nil	Nil	59·8	–	–	Oxalate/calcium 2 : 1 traces only of other constituents.
Mixed phosphate/oxalate									
(*a*) "Sterile"	25·3	9·0	Nil	Nil	Nil	35·8	–	–	Oxalate/calcium less than 2 : 1 phosphorus not more than 10% traces of Mg; NH_4, CO_3 absent.
(*b*) "Infected"	27·5	11·0	0·9	Nil	Nil	23·6	+	–	Oxalate/calcium 1 : 1: or less. Phosphorus 5% or more Mg, NH_4, CO_3 frequently present.
"Triple phosphate"	8·5	10·2	5·4	Nil	8·6	8·7	+	–	Mg/NH_4 1 : 1·3. CO_3 usually present. Sometimes small amounts of calcium and oxalate.
Apatite	32·5	16·5	2·3	Nil	Nil	8·0	+	–	Calcium often 30%. Phosphorus usually 10%. Mg, CO_3 often present.
Uric acid	1·9	3·3	Nil	80·0	Nil	Nil	–	–	Traces only of other constituents (except NH_4 in acid urate stones).
"Infected" uric acid	17·3	8·8	1·0	20·0	Nil	17·6	+	–	Diminished uric acid. Other constituents variable.
Cystine	Nil	Nil	Nil	Nil	Nil	Nil	–	+	Usually pure.
"Infected" cystine	14·3	7·8	0·4	Nil	Nil	Nil	+	+	One only found
Silica	1·4	0·8	0·5	Nil	Nil	6·7	–	–	Silica suspected from absence of other constituents. Comfirmed by reference laboratory (Joekes, Rose and Sutor, 1973).

surrounded by a soft proliferation of phosphate is supported by the chemical characteristics of staghorn calculi (Table II, Figs. 2 to 6).

It was, however, interesting to observe that even in terms of size and shape there was a marked difference depending on the sex of the patients. Table VI shows clearly that staghorns from women are very largely composed of triple phosphate, and that small stones from male patients are much more likely to be calcium oxalate than those from females.

6. *Recurrence of Stone Formation*

The degree to which a stone former is able to reproduce the pattern of chemical composition of the initial calculus depends to a large extent upon whether the urine remains sterile. This is demonstrated by the coefficients of correlation shown in Table VII. Applied to recurrent sterile calculi these are significant for each parameter studied; even the lowest coefficient exceeds its standard error by a factor greater than 5. One may conclude from this that for each patient liable to urolithiasis there is an inherent set of factors which determine the composition of the stone formed. A change in these factors, the most obvious being the onset of infection, alters the chemistry of the accretion. Stones of such mixed composition may differ not only from centre to surface but from one end to the other in large stones that obstruct the ureter.

In addition to the positive findings, a great deal of experience was gained as to the pitfalls into which this type of enquiry may fall through lack of patient data.

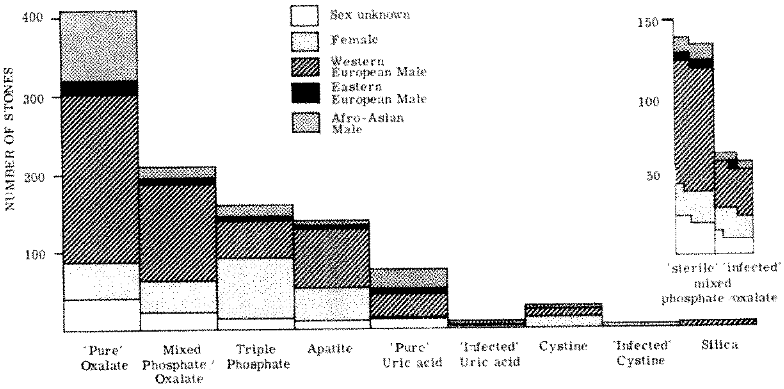

Fig. 8 Classification of calculi by empirical composition patterns.

In any further study, information will be sought on all the following variables: sex, age, country of origin and occupation of the donor; the clinical diagnosis of the underlying condition; and, if the calculus has been removed at surgery, the site of formation.

Conclusions

A correspondence was apparent between stone composition and the sex of the stone former. This is probably due to the greater risk in women of urinary infection, giving rise to the type of calculus which forms in an alkaline medium, typically magnesium ammonium phosphate or carbonate-apatite in composition and staghorn in shape. Children of both sexes tended also to form these types of stone. Environmental factors were less easy to evaluate, but it was found that Afro-Asian and Eastern European males formed more uric acid, more oxalate and fewer apatite calculi than Western males. It was also shown that small stones contain significantly more oxalate than larger stones.

In the 3 diagnostic states in which the stone chemistry was scrutinised, idiopathic hypercalciuria presented a very low proportion of triple phosphate or apatite-carbonate calculi. There was some evidence, at present inconclusive, that hyperparathyroidism favours the production of apatite stones.

Table VI

Percentage Distribution of each Stone Pattern in Types of Stone

Description or Source of Stone	Sex of Patient	Pure Oxalate	Mixed Phosphate/Oxalate		"Triple Phosphate"	Apatite	Uric Acid		Cystine
			"Sterile"	"Infected"			"Sterile"	"Infected"	
Total sample	212 Female 717 Male 95 Sex unknown	39·4	13·8	6·4	15·4	13·2	7·2	0·8	2·8
From adults	Female	22·2	9·4	8·4	35·1	17·8	1·0	0	5·9
From adults	Male	47·9	16·0	6·0	8·1	11·3	8·1	0·8	1·5
From Western Europeans	Male	45·4	19·1	6·6	7·7	11·0	8·3	0	1·5
From Eastern Europeans	Male	52·5	11·2	2·8	0	8·4	16·7	8·4	0
From Afro-Asians	Male	57·8	6·2	3·4	10·3	2·7	16·5	1·4	2·0
In hyperparathyroidism	19 Female 4 Male	17·4	30·2	17·4	0	34·8	0	0	0
In sponge kidney	5 Female 9 Male	35·8	28·7	14·3	0	21·3	0	0	0
In idiopathic hypercalciuria	1 Female 45 Male	52·2	39·1	0	0	6·5	0	0	0
From children	Female	18·0	0	0	25·0	18·8	0	0	37·5
From children	Male	8·7	8·7	4·3	52·2	21·7	0	4·3	0
Staghorn	Female	0	0	3·0	78·8	12·1	0	0	6·1
Staghorn	Male	17·2	6·9	17·2	37·9	10·3	3·4	0	6·9
Less than 100 mg	Female	25·0	8·3	16·7	19·4	19·4	2·7	0	8·3
Less than 100 mg	Male	55·5	18·4	3·0	2·6	9·0	9·8	1·3	0·4

Repeated stone formation appeared to follow a predetermined fashion. Providing that urinary infection did not occur between stones or during stone formation, successive stones from the same patients tended to be similar in chemical composition.

Table VII

Multiple Stone Formers: Initial Stone Composition compared to that of Subsequent Stones

Parameter	Correlation Coefficient in "Sterile" Stones	Correlation Coefficient in "Infected" Stones
Calcium	0·56	−0·19
Oxalate	0·80	0·85
Phosphorus	0·77	−0·11
Magnesium	0·90	0·52
Ammonium	0·90	−0·09

I am indebted to Dr G. A. Rose for encouraging and editing this survey. I must also thank Mrs E. G. Willden for permitting me to incorporate her own original work; Mr A. Constable for his advice on statistics; Mrs A. Barrett and Mr R. E. Bartholomew of the Institute of Urology, Miss Christine Simpson and Miss Bridget Harmston for invaluable assistance and patience in preparing the paper for publication. Not least, I must pay tribute to all the technicians, and in particular Mr P. Omenogor and Mr C. J. Woodfine, who have helped to perform all the analyses on which this study is based.

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Composition of Urinary Calculi by X-ray Diffraction. Collected Data from Various Localities. Parts XV-XVII

Royal Navy; Bristol, England; and Dundee, Scotland

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As part of our survey of the composition of urinary calculi on a regional and historical basis, we present here data for 3 collections from Great Britain. The X-ray powder method (Lonsdale, Sutor and Wooley, 1968) has been used to determine the amount and identity of the crystalline material in each stone, and the results are presented in the usual way to show the weighted percentage amount of each compound identified averaged over the whole collection, the percentage number of stones containing an observable amount of a compound, and the percentage number of stones grouped according to the type of components present.

XV. Royal Naval Hospital, Gosport, England

Because of the nature of the hospital, the 97 upper urinary tract calculi received came mainly from male patients. There are 92 males and 5 females having an age range of 18 to 80 years and an average age of 36·9 years. Most of the stones are small, and 95 of them have weights between 0·001 and 2·86 g, the average value being 0·16 g. The 2 other stones weigh 10·73 and 19·27 g. The latter is a staghorn infection stone from one of the female patients and the former is a uric acid kidney stone from one of the males.

The composition of the stones is shown in Tables I and II. The most abundant crystalline constituents are the 2 hydrates of calcium oxalate, each of which is present in over 80% of the stones and which together account for 77% of the total crystalline material in the collection (Table I). Rather unusually, the amount and frequency of occurrence of the dihydrate exceeds that of the monohydrate. Hydroxy- and carbonate-apatite are the only other important constituents, all other compounds present being minor components of the collection. Although hydroxyapatite occurs in 41% of the stones, it is a minor component of many since it accounts for only 11% of the total crystalline material. The most common types of stones are those composed of pure calcium oxalate (46% of the total number) and of calcium oxalate+calcium phosphate (45%). However, the weighted percentage amounts of the constituents show that the overall amount of calcium oxalate exceeds that of calcium phosphate in the latter variety. These 2 types of stones are the ones most commonly encountered in industrialised countries, but the relative proportions of each and hence of the main constituents vary in the different areas (Sutor and Wooley, 1971, 1972). In the collections from Northern Ireland (Sutor and Wooley, 1972), Glasgow, Scotland (Sutor and Wooley, 1971), and Dundee (see later), the mixed calcium oxalate+calcium phosphate stones have predominated. Other composition types in the present collection account for only a small proportion of the total number of stones.

Most of these upper urinary tract stones consist of aggregates of crystals with no obvious

Table I

Composition of the Stones

Collection	Type	No. of stones	A1	A2	B	J	C1	C2	F1	F2	F3	F4	F5	G1	G2	X
			(a) Weighted percentage of the constituents													
Royal Navy	Upper tract	97	1	1	...	...	30	47	7	11	...	>0	...	...	1	1
Bristol	Upper tract	87	...	...	...	...	42	25	12	11	>0	2	1	>0	7	...
Dundee	Upper tract	90	>0	>0	...	...	26	26	21	14	...	2	...	>0	11	>0
	Lower tract	31	5	3	4	>0	21	12	26	5	6	...	>0	...	18	...
			(b) Percentage occurrence of constituents													
Royal Navy	Upper tract	97	3	2	...	...	84	85	11	41	...	1	...	...	2	1
Bristol	Upper tract	87	...	...	...	...	78	62	22	38	1	8	3	1	20	...
Dundee	Upper tract	90	1	1	...	...	61	58	37	38	...	4	...	2	27	3
	Lower tract	31	16	10	23	3	45	42	55	16	10	...	3	...	48	...

Key: A1 = anhydrous uric acid, A2 = uric acid dihydrate, B = ammonium acid urate, J = sodium acid urate monohydrate, C1 = calcium oxalate monohydrate, C2 = calcium oxalate dihydrate, F1 = carbonate-apatite, F2 = hydroxyapatite, F3 = brushite, F4 = whitlockite, F5 = octacalcium phosphate, G1 = newberyite, G2 = struvite, X = unidentified material, C = C1 and/or C2, F = any combination of F1, F2, F3, F4 and F5, etc.

Table II

Percentage Number of the Types of Stones classified according to the Compounds Present

	Percentage in Collections from			
Type	Royal Navy	Bristol	Dundee (upper tract)	Dundee (lower tract)
A1	1·0	...	...	...
A1+A2	2·1	...	...	3·2
C1	5·1	11·5	4·4	3·2
C2	5·1	2·3	1·1	...
C1+C2	36·1	25·3	22·2	9·7
F	2·1	3·5	6·7	3·2
G2	...	1·2	1·1	...
A+B	...	...	...	3·2
A+C	...	...	1·1	9·7
B+F+G	...	...	...	12·9
B+G	...	...	...	3·2
B+J+F+G	...	...	...	3·2
C+F	45·4	37·9	34·4	19·4
C+F+G	...	3·4	4·4	9·7
C+F+X	...	...	2·2	...
C+G	...	...	...	3·2
F+G	2·1	14·9	21·1	16·1
F+G+X	...	...	1·1	...
X	1·0	...	...	...

Key as for Table I.

nuclear region, so a comparison of the composition of the nucleus with that of the rest of the stone could not be made.

XVI. Bristol, England

We received 87 upper urinary tract stones. They came from 63 male and 23 female patients (the sex of 1 was not provided) with an average age of 45·5 years and an age range of 3 to 81 years. Only 4 of the patients were under 21 years and their age range was 3 to 9 years. The calculi range in weight from 0·0001 to 12·71 g and have an average value of 1·07 g. However, only 11 of them weigh more than 2 g and if these are excluded, the average stone weight is 0·34 g.

The most important crystalline constituents are again the calcium oxalates but they are found in fewer stones compared with the previous collection and account for only 67% of the total crystalline material (Table I). The apatites rank next in frequency of occurrence and abundance, and they are followed by struvite which is a constituent of 20% of the stones. The decrease in the amount of calcium oxalate is a result of an increase in that of struvite and carbonate-apatite. The most important types of stones consist of calcium oxalate (39% of the total) and calcium oxalate+calcium phosphate (38%) but 15% of the calculi in this collection consist of calcuim phosphate+struvite (Table II). No other composition type constitutes more than 3% of the total.

XVII. Dundee, Scotland

We received 90 upper and 31 lower urinary tract stones which have been treated as 2 separate collections. The upper tract stones came from 55 males and 35 females whose average age was 40·8 years and whose age range was 2 to 74 years. Only 9 of the patients were under 21 years and their age range was 2 to 18 years. These stones weigh between 0·005 and 29·67 g and have an average weight of 1·64 g. Again most of the stones (70) are less than 2 g and their average weight is 0·33 g. The patients with lower urinary tract calculi consist of 23 males and 8 females with an age range of 2 to 89 years and an average value of 58·1 years, which is greater than that for the patients with upper tract calculi. There are only 2 children in this group and their ages were 2 and 15 years. Although some stones are small, in general the lower tract calculi tend to be larger than the upper tract ones and their average weight is 6·40 g and their weight range 0·008 to 57·87 g.

The composition and types of stones for both sites are given in Tables I and II. In the case of the upper urinary tract stones, the calcium oxalates are again the most important constituents, and both hydrates contribute the same amount of crystalline material and are present in approximately the same number of stones (Table I). There is a greater amount of the apatites and struvite than in the other collections of upper tract stones reported in this paper, and this is reflected in the percentage amounts of the types of stones. Those composed of calcium oxalate+calcium phosphate and pure calcium oxalate comprise 34% and 28% of the total number in the collection and are again the most important varieties, but a large proportion (21%) consists of calcium phosphate+struvite (Table II). Eight of the 9 children's stones belong in this group, the other is composed of calcium oxalate+calcium phosphate. About 7% of the calculi consist of pure calcium phosphate but each other type makes up less than 4% of the total number of stones.

The composition of the lower urinary tract stones is not nearly so well defined as that of the upper tract ones. Carbonate-apatite is the most abundant and frequently occurring constituent and the total amount of calcium phosphate exceeds that of calcium oxalate (Table I). Struvite also occurs in a high proportion of the stones, and the uric acids and urates which are very rare constituents of the other collections reported here are found in several of these lower tract calculi. There are many different types of stones in this collection (Table II). The mixed calcium oxalate+calcium phosphate variety is the most common one, but it accounts for only 19% of the stones and is closely followed by the calcium phosphate+struvite type (16%), the pure oxalate one (13%) and that composed of calcium phosphate+struvite+ammonium acid urate (13%). The latter type appears to form in urine infected by a urea-splitting organism and saturated with uric acid. So infection calculi formed in urines of different composition are likely to be the most important lower urinary tract stones.

Summary

An X-ray diffraction study of the composition of upper tract urinary stones from 3 centres in Great Britain shows that the calcium oxalates and the calcium phosphates are the most abundant and frequently occurring crystalline constituents, and that the most common varieties of stones are those composed of pure calcium oxalate and calcium oxalate+calcium phosphate. The relative proportions of these types, however, vary in the different areas.

Infection stones consisting of struvite+calcium phosphate are the next important type in the collections from Bristol and Dundee, but there are few of these stones in the collection from the Royal Navy.

In a small collection of lower urinary tract calculi from Dundee, stones composed of calcium oxalate+calcium phosphate again predominate, but they are exceeded by infection stones if the different varieties of these are grouped together.

Whereas a few composition types dominate the collections of upper urinary tract calculi, there are many more combinations of constituents found in the collection of lower tract stones.

We are very grateful to Surgeon Commander N. J. Blacklock for supplying us with the calculi from the Royal Naval Hospital, to Mr R. C. L. Feneley who supplied those from Bristol and to Mr J. Grieve who supplied those from Dundee.

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Muco-epidermoid Carcinoma of the Penis

Report of an Unusual Case

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The most common tumour occurring in the penis is squamous-cell carcinoma. In the majority of cases it is a well-differentiated carcinoma arising in the glans or in preputial skin. At the Tata Memorial Hospital, during the years 1941 to 1972, there are records of 1,553 histologically proven cases of carcinoma of the penis. Besides squamous-cell carcinoma, uncommon tumours of the penis reported by us are malignant melanoma (Sirsat and Shrikhande, 1965) and collision tumour (Shrikhande and Sirsat, 1969). In this paper we report the muco-epidermoid carcinoma of the penis so far not reported in the literature.

Case Report

A Hindu male, aged 40 (no. AD-8347), was admitted to the Tata Memorial Hospital, Bombay, on 28th July, 1972, complaining of a fungating growth destroying the major portion of the penis. The duration was 1 year. Lymph nodes in both inguinal regions were palpable. Radiological examination of the lungs did not show any evidence of metastases. Total amputation of the penis with bilateral orchidectomy was carried out on 2nd September 1972. His postoperative progress was uneventful and he was discharged on 12th September 1972. He was readmitted for excision biopsy of an inguinal lymph node on 28th November 1972. There is no further follow-up.

Pathology

Gross Observations. Specimen received in the laboratory consisted of the whole penis with both testes. There was a fungating growth completely destroying the glans penis, measuring 8 cm in the long axis. The cut surface of the growth showed greyish white opaque appearance (Fig. 1). Neither testes showed any pathological changes. There was a group of lymph nodes removed from the left inguinal region, the largest node measured 4·5 × 1·5 cm. The cut surface showed glistening opaque greyish-white tumour replacing the lymphoid tissue.

Microscopic Findings. Several sections were taken for histological examination. The tumour consisted of groups of polygonal epidermal cells separated by connective tissue strands which showed infiltration by mononuclear inflammatory cells. The majority of the nuclei of the tumour cells were vesicular but a few were hyperchromatic and showed mitotic figures. Besides this, there were groups which appeared acinar in structure (Fig. 2). The cytoplasm of these cells and lumina contained bluish material which was identified as mucin with special stains (Fig. 3).

Microscopic examination of the lymph nodes showed metastasis of both epidermal element which was predominantly seen and mucin-containing cells such as were seen in the primary tumour (Fig. 4).

Discussion

The common type of carcinoma of the penis is of squamous-cell variety and arises from the epithelium covering the glans or the preputial skin. A muco-epidermoid carcinoma occurring in the penis on the other hand probably arises from the glands around the urethra, the glands of Littré. Lower and Hausfeld (1947) have reported 10 cases of primary carcinoma of male urethra. In their series 1 was a mucinous carcinoma of the signet-ring type but was not of muco-epidermoid variety.

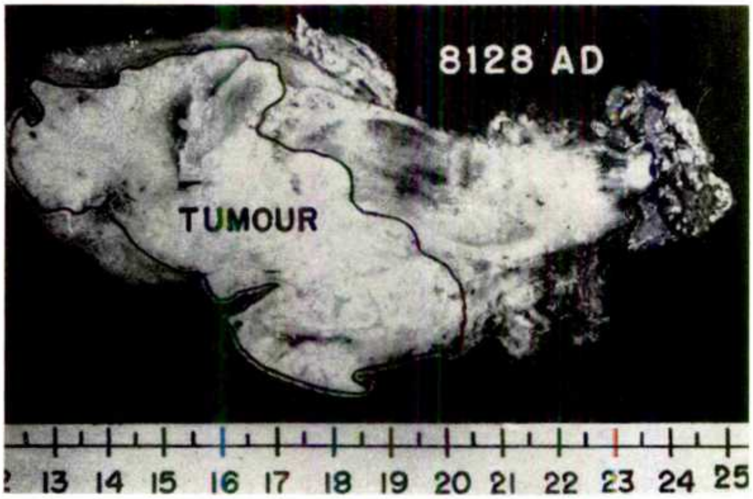

Fig. 1. A specimen of cut surface of the penis showing a greyish white opaque tumour.

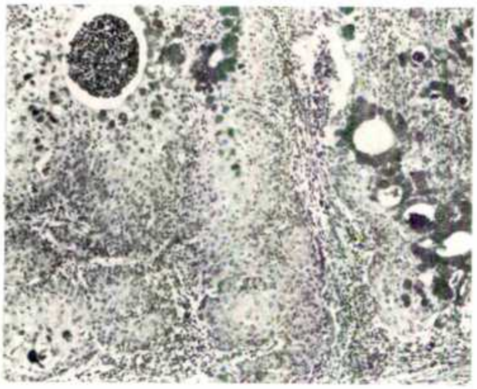

Fig. 2

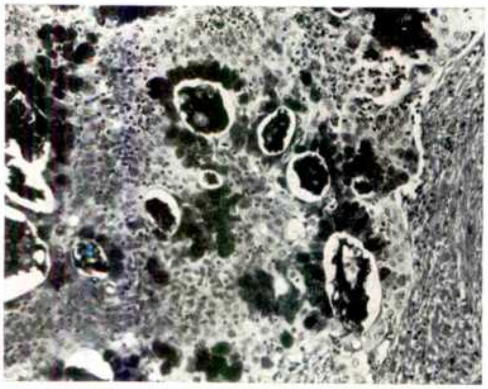

Fig. 3

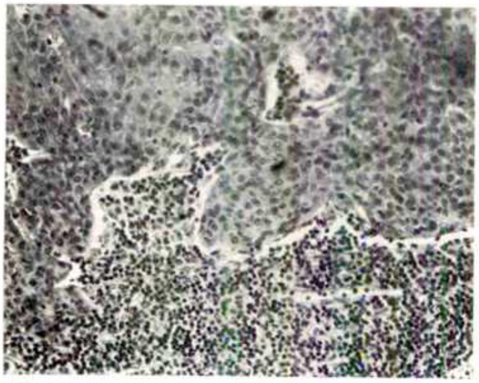

Fig. 4

Fig. 2. Photomicrograph showing areas of epidermoid carcinoma and acinar cells showing bluish stained cytoplasm containing mucin. (H & E stain. × 212).

Fig. 3. Photomicrograph showing tumour cells with presence of mucin. (Mucicarmine stain. × 334).

Fig. 4. Photomicrograph of lymph node showing metastasis of the tumour. In the metastatic node the epidermoid areas were predominant. (H & H stain. × 334).

Histologically glands of Littré arise as out-pocketings from the lacunae of Morgagni. These glands are mainly lined by pseudostratified columnar epithelium but at places nests of clear cells are seen within the epithelium which show positive reactions for mucin (Bloom and Fawcett, 1968).

Muco-epidermoid tumour primarily occurs in the salivary gland and was recognised as a separate entity by Stewart *et al.* (1945). The other reported uncommon sites are lung (Kreyberg, Liebow and Uehlinger, 1967), cervix (Hamperl and Hellweg, 1957), nasal mucosa and larynx (Ringertz, 1938), anus (Kay, 1954) and oesophagus (Weitzner, 1970). We have reported up till 1968, 10 cases of muco-epidermoid carcinoma of the salivary glands (Shrikhande and Sirsat, 1970). In addition there was 1 in the lung and 1 in the larynx. We are of the same opinion as Hamperl and Hellweg (1957) who have concluded that muco-epidermoid carcinomas occur as a manifestation of a 2-fold differentiation potentiality of columnar cells into epidermoid and mucous cells.

Summary

A case of muco-epidermoid carcinoma of the penis in a Hindu male aged 40 is reported because of its rarity. It is the first case seen at the Tata Memorial Hospital during the past 30 years.

Our thanks are due to Doctor F. K. Mostofi for comments on the slides.

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Local Excision of a Virilising Leydig-cell Tumour of the Testis

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The commonly accepted approach in the treatment of testicular tumours consists of radical orchidectomy with high ligation of the spermatic cord. While agreeing in general with this policy, we were obliged, in the case considered hereunder to perform exploration and local excision and local excision of a virilising intra-testicular tumour.

Case Report

The patient was referred to our out-patient clinic at the age of 6½ years, in September 1969, because of precocious sexual and bodily development.

His past personal and family history were non-contributory. Until the age of 4½ years he had shown normal physical and mental development. Since then his parents had noticed the appearance and progressive increase of pubic and scrotal hair, simultaneous with an acceleration of general bodily growth. In addition the child had frequent erections.

On Examination. In contrast to his chronological age (6½ years) the patient had the physical appearance of a boy aged 10½ to 11 years (Fig. 1). He showed well-developed musculature. His height was 135 cm (compared to the average normal for 6½ years: 123 cm). He weighed 35 kg (average normal weight for his age: 25 kg). The scrotum was well developed with increased pigmentation of the skin and marked growth of pubic and scrotal hair (Fig. 2).

The size of the right testis was twice that of the left, its consistency somewhat firmer, and its surface not quite as smooth. The spermatic cord appeared normal and no lymph nodes were palpated. The penile length was 65 to 72 mm compared to the normal average of 35 to 45 mm for his age. On rectal examination there was no enlargement of the prostate. Physical examination was otherwise normal. Skeletal X-ray examination showed that his osseous age too, was advanced, being compatible with that of 11 years.

Hormonal Urine Assays (24 hours' excretion)
Testosterone: 7·3 μg/24 hours (normally undetectable).
Pregnantriol: 0·5 mg (within normal limits).
Oestrogens: 1 μg (within normal limits).
17-Ketosteroids: 1·2 mg (within normal limits).

X-rays of skull, chest, serum electrolytes, urea glucose, blood count and sedimentation rate were within normal limits. Because of the suspicion of an androgen-secreting tumour in the right testis we recommended inguinal exploration with a view to right orchidectomy, but in spite of repeated explanations the parents adamantly refused orchidectomy and consented only to a limited biopsy.

At operation (September 1969), on incising the tunica albuginea of the right testis at its inferior pole, a rounded, well-defined brownish-grey elastic nodule measuring 1 × 0·7 × 0·5 cm bulged forth from the rather softer surrounding tissue. The nodule was excised together with a thin margin of normally appearing tissue and in addition another smaller firmer nodule from the middle part of the right testis was also excised.

Histological examination of the first nodule showed a uniform structure of densely compressed polygonal cells with fine eosinophilic cytoplasm including fat vacuoles and rounded eccentric nuclei. The nodule was devoid of a capsule, but sharply defined from the rim of surrounding normally appearing testicular tissue, which showed scattered tubules but no signs of precocious spermatogenesis. The second nodule showed only fibrous tissue. The diagnosis was interstitial (Leydig) cell tumour without signs of malignancy (Fig. 3).

The postoperative course was uneventful. Repeated examinations during the ensuing 3 years showed no further increase of masculinisation. The child, now aged 9½ years, shows a bone age consistent with that of 12½ years, and his height corresponds to that of a boy aged 11½ years.

The urinary testosterone levels fell postoperatively to 2·4 μg/24 hours and recent repeated examinations could not reveal detectable amounts of this hormone; 17-ketosteroids, pregnantriol and oestrogens remained normal.

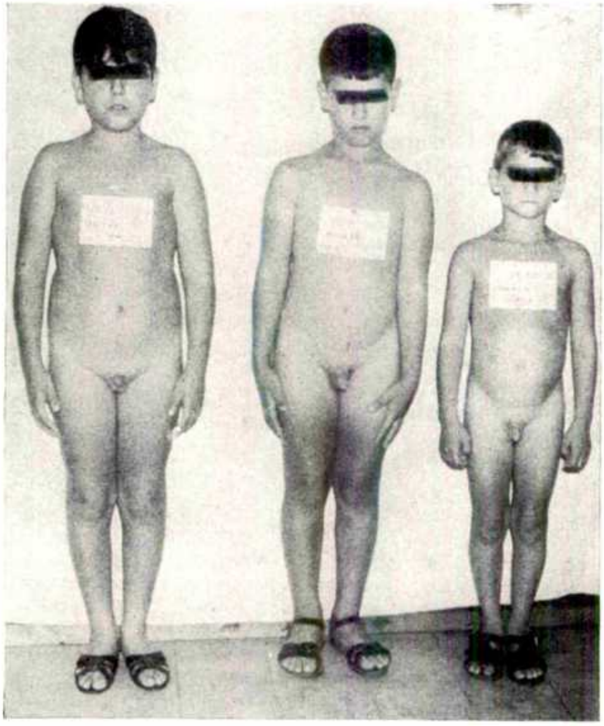

Fig. 1. Physical appearance of patient (centre) compared to normal boy aged 6 years (right) and boy aged 11 years (left).

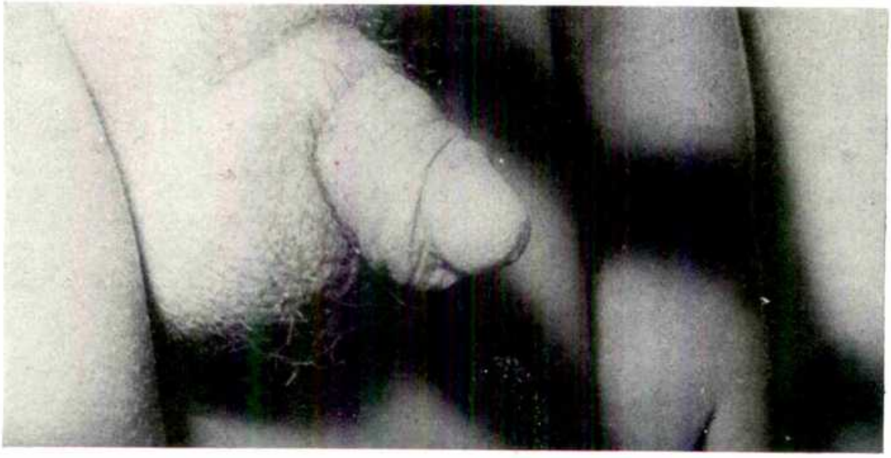

Fig. 2. External genitals showing prococious penile development with pubic hairs.

Discussion

The diagnosis in our case was made 2 years after the appearance of the first clinical signs and was based on precocious physical and sexual development, the histological finding on testicular biopsy, and the high level of urinary testosterone. There were no hormonal findings suggestive of suprarenal hyperactivity or chorion-carcinoma of the testis. Neither were there histological signs of precocious spermatogenesis as described by Gittes *et al.* (1970) nor testicular atrophy as described in adults by Blundon, Russi and Bunts (1953).

The operation performed 3 years ago was, according to our best judgement, inadequate and is considered so by most authorities. The follow-up in this case, however, has so far shown arrest of the pathological androgenic activity. During these 3 years bodily growth and bone age have progressed at a slower rate (two-thirds of the expected normal rate). The postoperative results indicate probable cure of the condition in our patient, in spite of the limited excision, and suggest the possibility of conserving testicular tissue in similar cases especially in the presence of single testes. In spite of the benign histological appearance of the tumour in our case and the low incidence of malignancy of interstitial cell tumour (less than 10%) metastases have been found as late as 9 years following resection of the primary tumour (Silverberg *et al.*, 1966; Hopkins, 1970). Johnstone (1967), on the other hand, found no metastases among 39 cases in prepubertal cases. Gittes *et al.* (1970), too, found that these tumours in children were all benign.

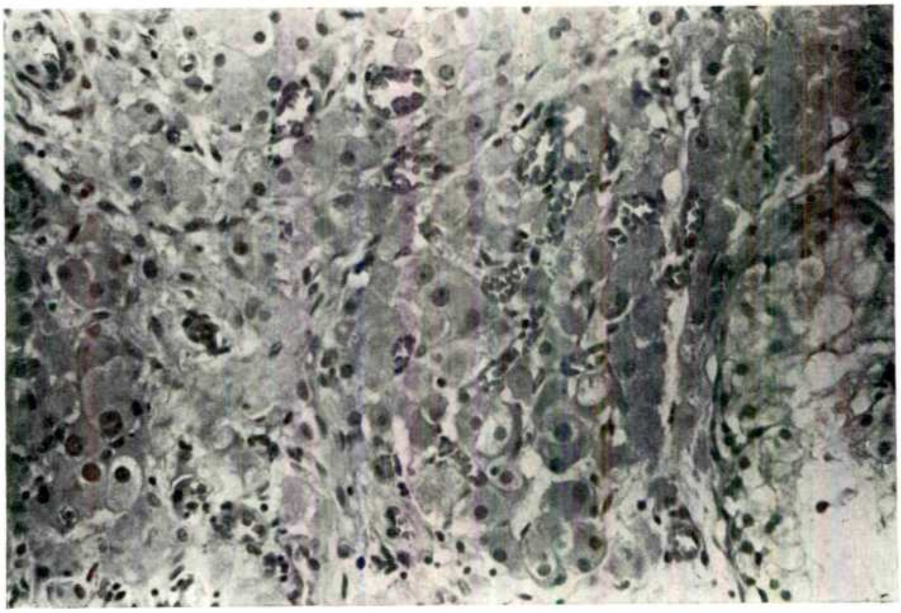

Fig. 3 Microscopic appearance of testicular tumour.

Further follow-up of our case is necessary to prove whether the treatment was adequate.

Summary

A boy with interstitial cell tumour of the testis producing precocious virilisation was treated by local excision with subsequent arrest of the pathological process.

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Conferences and Courses

The Sixth International Congress of Nephrology will be held June 8-12, 1975 at the Palazzo dei Congressi in Florence, Italy.

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Book Reviews

Osteomalacia, Renal Osteodystrophy and Osteoporosis. By BRIAN MORGAN. Pp. xvi+422 with 59 illustrations. Springfield, Ill.: Charles C Thomas. 1973. £8·88.

The scope of this book is even more restricted than its title suggests, for it is largely concerned with the chemical aspects of what the author is pleased to term "the three disorders of calcium metabolism: osteomalacia, renal osteodystrophy and osteoporosis". It opens with a review of calcium, phosphorus and bone metabolism which emphasizes—some will think over-emphasises—the importance of the kidney in calcium homeostasis. This is followed by sections on osteomalacia and renal osteodystrophy which are excellent as far as they go but omit any description of rickets or of the special problems which arise when renal osteodystrophy starts in childhood. The final section on osteoporosis reveals all too clearly that little of real importance has been gained from recent research into this ill-defined disorder. This is undoubtedly a scholarly work; the bibliography lists nearly 1200 learned papers and it is clear that the author has read and digested all of them. However one cannot help feeling that the text would have been easier to read, and less confusing, if the author had adopted a more selective approach. This book will undoubtedly prove to be a valuable work of reference for clinicians and medical scientists with a major interest in skeletal disorders, but it is doubtful whether it will appeal to those whose main interests lie elsewhere.

A. R. H.

A Colour Atlas of Renal Diseases. By GEORGE WILLIAMS. Pp. 240 with 285 illustrations. London: Wolfe Medical Books. 1973. £4·00.

This is a compact atlas of renal diseases which consists of photographic illustrations of gross and microscopic appearances of most of the medical and surgical disorders of the kidney. There are 16 sections and subsections, each preceded by a short explanatory text. The text is brief and sensible, but in some instances inadequate. The illustrations are well reproduced, although the degree of magnification in a few of the microphotographs is insufficient and uninformative. It is irritating to find that 5 photographs of gross specimens are either printed upside down or back to front. The book is intended to provide "a better understanding" of renal disease and is aimed at undergraduates. In this respect it has achieved its object. Its price, by today's standards, is modest.

P. E. P.

ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

Acta Urologica Japonica

By D. I. Roberts

"Exfoliative Cytology and Chromosomal Analysis in Tumor of the Bladder by Pumping Method." T. Nagayama and S. Kataumi. (1972, **18**, 5-11)—The authors performed this study at Chiba University. After catheterisation, pumping irrigation of the bladder was performed and a stained preparation made from the sediment of the centrifuged irrigation fluid. Positive cytological diagnosis was made in a number of cases and chromosome analysis of the exfoliated tumor cells was made in a few cases.

"Effect of Antiserum on Peripheral Blood Lymphocyte." T. Abe, H. Kusumi, T. Inoue and M. Kanazawa. (1972, **18**, 110-112.)—From Wakayama Medical College comes a report dealing with locally prepared ALS. Studies were made on a renal transplantation patient and control studies on three other patients and these showed that ALS depleted the large lymphocytes. ALS may act by (1) lymphocyte depletion, (2) interfering with immunologic process by coating the lymphocytes, (3) acting as a competitive antigen.

"Clinical Studies on Radioisotope Renogram. Part II. Studies on Quantitative Analysis." H. Ueyama. (1972, **18**, 113-132.)—Quantitative mathematical analysis of the renogram curve was made at Kyoto University. Semi-quantitative methods compare the amplitude of the curve at different times. Advanced mathematical analysis based on compartmental analysis of the curve by computer has been shown to be clinically useful in over 5000 cases. Digital simulation is more convenient than analog simulation in the application of this method.

"Treatment of Urinary Incontinence by Electric Simulator." K. Nakaavai and T. Sonada. (1972, **18**, 257-274.)—At Osaka University, an electrical stimulator using a 22·5 V battery and either surface or pessary electrodes was developed. The surface electrodes were applied over the pudendal nerve medial to the ischial tuberosity. In 5 cases of neurogenic bladder dysfunction and 3 cases of stress incontinence the stimulator produced satisfactory tightening of the external vesical sphincter. Accompanying photographs show that the plate electrodes can be conveniently worn under a pair of underpants.

"Experimental Studies on Kidney Function and its Recovery, after Complete Chronic Unilateral Ureteral Obstruction." C. Ohyama. (1972, **18**, 373-390.)—At the Kyoto University 38 dogs were submitted to unilateral ligation of the ureter for periods from 10 to 60 days. The ligature was then released and renal function was evaluated immediately and 2 months later. Up to 20 days, full recovery of the obstructed kidney occurred although the immediate post obstruction function was much diminished. At 30 days the 2 month recovery was 50%, whilst after 50 days, no recovery occurred after 2 months.

"Effect of Mesterolone on Male Sterility." M. Shirai, M. Takeuchi and K. Sasaki. (1972, **18**, 442-446.)—Methylandrostanolone was administered to 40 men in a dose of 30 mg daily to a total dose of between 900 and 6000 mg. All men initially had oligospermia and in 60% the sperm concentration increased after treatment. 4 pregnancies resulted. In 7 cases, there was evidence that the drug had a central inhibiting action with a rebound phenomenon when it was discontinued. This work was performed at Tohoku University.

"A Study of Male Infertility with Special Reference to Sex Chromatin and Sex Chromosome." Y. Nagahama. (1972, **18**, 477-500.)—An excellent paper from Kobe University. 598 patients attending a male infertility clinic received the sex chromatin test. The chromatin positive males underwent testicular biopsy, seminal vesiculography, chromosome analysis and determination of urinary hormones. Figures and diagrams showing the results of these investigations are presented. 3·2% of the patients were found to be chromatin positive.

"Transient Renal Infarction in Selective Renal Arteriography." J. Kawamura *et al.* (1972, **18**, 539-562.)—Aortography was performed on 2 cases of essential haematuria and showed normal renal arteries. In both cases, subsequent selective renal arteriography showed obstruction of one of the arterial tributaries. Renal function of the affected side was monitored by IVP, renogram and renoscintigram and found to return to normal after 6 months. This work is from Kyoto University.

Annals of Surgery

By J. E. A. Wickham

"Repair of the Ureter Severed at Operation." Chomchark Chuntrasakul, M.D. (1973, **177**, 748-757.)—This paper describes the experimental results in 6 dogs, coupled with 2 human case reports on the repair of the severed ureter. Experimentally dog ureters were transected and then resutured with either 6 "O" polypropylene or 6 "O" mersiline sutures or 6 "O" silk. In both the human cases 6 "O" silk was the anastomotic material. All dogs and both human cases healed their ureters excellently with no stricture and no evidence of calculus formation on any mucosal surface or at the anastomotic line. It is suggested that complete transection of the ureter should be treated by direct end to end anastomosis and with interrupted non-absorbable sutures without splinting.

"Ten Years Experience with the Surgical Management of Renovascular Hypertension." John H. Foster *et al.* (1973, **177**, 755-766.)—The paper reviews the treatment of 1070 hypertensive patients over a 10-year period. 464 patients were found to have renal artery stenosis and of these, 39% had renovascular hypertension proven. Of these 176 patients, 148 had operative treatment. There were 8 operative deaths in the series. Aorto-renal by pass graft was the most common technique. 90% of these patients who were operated on were either cured or improved. Patients with fibromuscular dysplasia did better than patients with atherosclerotic lesions. In the course of the study it was concluded that (1) renovascular hypertension is a fairly common condition; (2) that history and physical examination are not helpful in differentiating essential hypertension from renovascular hypertension: (3) renal arteriography including selective oblique study is the best screening test; (4) if a renal arterial occlusive lesion is found then renal function studies and renal venous renin assays should be done to determine the significance of the lesion; (5) if all these tests are positive, a beneficial result can be expected to follow in 80% of cases.

The Australian and New Zealand Journal of Surgery

By H. H. PEARSON

"Carcinoma Associated with Renal Tuberculosis: A Report of Two Cases, with a Brief Review of the Literature." M. L. MEHROTRA, I. M. GUPTA, N. N. KHANNA and SAROJ GUPTA. (1973, **43**, 58-60.)—From the Departments of Pathology and Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, comes the report of 2 cases of carcinoma and renal tuberculosis occurring in the same kidney. Neibling and Walters (1948) had reported 7 cases and reviewed the previous reported 19 cases, a total of 26 up to that time. No account of co-existence could be found in the Indian literature although individually both diseases are fairly common. The authors point out that the inter-relationship between tuberculosis and cancer has been of interest in organs other than the kidneys and that experimentally the existence of tuberculosis appears to render an organ less susceptible to the development of cancer. In the 2 cases presented, renal tuberculosis was not considered in the clinical diagnosis, the pressing features being those of renal carcinoma. They conclude that the co-existence in the present 2 cases appears coincidental.

"The Fate of the Remaining Kidney in 73 Patients Subjected to Nephrectomy for Renovascular Hypertension." EMMANUEL VLAHAKIS. (1973, **43**, 114-117.)—The author now in Adelaide reviews the histories of 146 patients subjected to nephrectomy for renovascular hypertension at the Mayo Clinic between the years 1955 and 1969. From this group 73 patients were selected on the basis of adequate data concerning renal function before and after operation. The aetiology of the renal artery stenosis was atheroma in 35 and fibromuscular dysplasia in 38. The 73 patients were divided into 3 groups: (1) unilateral arterial disease treated by nephrectomy—35; (2) bilateral arterial disease, the worst side being treated by nephrectomy with either concomitant or subsequent contralateral arterial repair—15; and (3) bilateral arterial disease, the worst side only being treated by nephrectomy—23. The patients were followed from 1 to 10 years with an average of 5. In 42% the remaining kidney underwent functional and morphological hypertrophy, in 24% kidney function remained unchanged and in 34% chronic renal failure developed. The prognosis was found to be better with fibromuscular disease than with atheroma. The presence of mild to moderate arterial disease in the remaining kidney did not significantly affect its function.

Indian Journal of Surgery

By R. T. BURKITT

"Strangulating Injury of the Penis." G. S. CHAPLOT. (1973, **35**, 244-246.)—The author describes 2 appalling cases of little boys who had strings tightly tied round their penis with resultant strangulation. In each case the cord appears to have been so tight that it cut right through to the urethra, virtually dividing the penis in half. Despite this, however, plastic repair appears to have produced a completely normal penis in each case with full function.

Spanish Journal of Urology

By C. A. C. CHARLTON

"A Contribution to the Study of the Ureteral Membrane of Chwalla. Its Clinical Importance." G. DOMENECH RATTO, A. TEJEDO MATEU and J. VILANOVA TRIAS. (1973), **26**, 355-372.)—During foetal development, the ureter as it traverses the bladder wall has its lumen occluded for a period of weeks by a membrane named after its discoverer in 1927, Chwalla. The authors examined 50 human embryos and foetuses of between 9·5 and 89 mm in length. They found Chwalla's membrane to be present in the 15 specimens of between 35 and 50 days gestation (12 to 43 mm in length). The membrane appears to be absorbed after this time. Since the foetal kidney does not secrete urine for the first 70 days of intra-uterine life, the ureteral obstruction is of no consequence. However, if the membrane should persist during the time of urine production, dilatation of the upper urinary tract on that side would presumably result. The authors suggest this mechanism accounts for idiopathic congenital megaureter and the non-obstructive congenital uretero-hydronephrosis.

"Ileo-caeco—cystoplasty." F. HIDALGO C., S. MIRELMAN W., and L. HIDALGO C. (1973, **26**, 437-450.)—The authors describe their results with 11 selected cases (10 tuberculous) undergoing ileo-caeco cystoplasty by the Gil Vernet technique. The tuberculous cases had all had a previous nephrectomy, had systolic bladders and a dilated upper tract with reflux. The blood chemistry was normal in all cases (8 had nephrostomies). Bladder capacity was less than 100 ml (in half the cases less than 50 ml), but there was no outflow obstruction in any case. The cut end of the ascending colon was anastomosed to the "unroofed" bladder. The dilated ureter anastomosed to the ileal end of the bowel segment. The bowel continuity was re-established by an end-to-end anastomosis of ileum to ascending colon. The greatest benefit experienced by the patients was with reduced urinary frequency. Urinary infection is a considerable problem. Blood chemistry is virtually unaltered.

Surgery, Gynecology and Obstetrics

By Thomas Moore

"Radionuclide Postpartum Evaluation of the Urinary Tract during Anovular Therapy." JACK D. CLAYTON and JAMES A. ROBERTS. (1973, **137**, 215-219.)—Combining radioactive renography with concomitant polarised serial scintiphotos of the kidney the authors have studied renal and ureteric function in 35 postpartum primigravidas. 10 have had a normal pregnancy and 25 had suffered from pre-eclampsia, concomitant or previous urinary infection. By this method they were able to demonstrate abnormal renal and ureteral function after the intravenous urograms had returned to normal and that this lasted longer in those patients who had suffered from pre-eclampsia.

"Urinary Excretion of Cyclic Adenosine Monophosphate in the Detection and Diagnosis of Primary Hyperparathyroidism." H. SCHMIDT-GAYK and H. D. ROHER. (1973, **137**, 439-444.)—The authors give a detailed account of their investigations into the excretion of cyclic adenosine 3′,5′ monophosphate in 9 patients with primary hyperparathyroidism and 27 controls. They believe the best diagnostic test of the disease is the excretion of the drug relative to the amount of creatinine, micromoles per gram of creatinine.

"Bilateral Nephrectomy performed on an Emergency Basis for Life-threatening Malignant Hypertension." ALAN H. BENNETT and J. MICHAEL LAZARUS. (1973, **137**, 451-452.)—The authors from extensive experience at Peter Bent Brigham Hospital, Harvard Medical School, Boston, believe that some of the more severe hypertensives with threatening cerebral, cardiac, renal and eye complications and high serum renin levels without renal arterial stenosis are best treated by early bilateral nephrectomy and subsequent regular dialysis. In the past 3 years they have treated 12 such patients who did not respond to haemodialysis and drug therapy; all recovered with minimal morbidity and have now either been successfully transplanted or are well controlled on a chronic dialysis programme.

"Endoscopic Suspension of the Vesical Neck for Urinary Incontinence." THOMAS A. STAMEY. (1973, **136**, 547-554.)—The very well known author from the University of Stanford, California, describes a new method for the treatment of stress incontinence. Using specially designed needles, a heavy monofilament loop of nylon is passed through a small lateral suprapubic incision at each side of the bladder neck to suspend it. Under endoscopic control, the posterior quadrant can be seen to be raised and the exact vesical neck closed. The author stresses the importance of the very exact siting of the slings at the bladder neck and not in the proximal urethra. Suprapubic drainage is instituted for a few days. The results in 16 patients who had previously had 29 operations for cure, though 5 were still totally incontinent, have been encouraging.

"Carcinoma of the Female Urethra." R. A. BLATH and F. H. BOEHM. (1973, **136**, 574-576.)—Between 1952 and 1972, 180,000 female patients were admitted to the Obstetrics and Gynaecology Department of the Vanderbilt University Hospital, Tennessee. 8 patients who suffered from carcinoma of the urethra were treated by operation or radiation, or both. There were 4 5-year survivors.

"Permanent Nephrostomy by Cutaneous Inversion." CHARLES E. BELLINGHAM and MAXWELL MALAMENT. (1973, **136**, 624-626.)—The principle of this method is that after the nephrostomy tube has been inserted into the lower calyx, a rectangular flap of skin is cut on each side of the wound at the preferred site of its emergence. Fat and subcutaneous tissue is removed from these skin flaps, each of which is sutured to the renal capsule, forming a skin tube surrounding the nephostomy opening. The authors state that this method allows easy replacement of the tube and avoids secondary irritation and infection of the surrounding skin.

"Experience with Renal Transplantation in High Risk Patients." JOHN E. WOODS, CARL F. ANDERSON, WILLIAM J. JOHNSON, JAMES V. DONADIO Jr., PETER P. FROHNERT, FRANK J. LEARY, JAMES D. DEWEERD and HOWARD F. TASWELL. (1973, **137**, 393-398.)—The authors analyse 48 cases of renal transplants carried out at the Mayo Clinic for terminal renal failure in particularly high risk patients. These were grouped as: (1) those with diabetes mellitus; (2) those with a history of gastrointestinal bleeding or peptic ulcer diathesis; (3) patients with pre-formed antibodies to 15% or more of a random lymphocyte population; (4) cadaveric allograft recipients 45 years of age or older; (5) living related donor recipients 55 years of age or older; (6) obese patients; (7) patients with major extrarenal problems. From their experience they conclude that the only ones with significantly high risk are those recipients of cadaveric kidneys older than 45 years and those with pre-formed antibodies. Patients having both adverse factors carry an extremely high risk both in terms of graft and patient survival.

"Polycystic Renal Disease Treated by Renal Transplantation." OSCAR SALVATIERRA Jr., SAMUEL KOUNTZ and FOLKERT O. BELZER. (1973, **137**, 431-434.)—From the Transplant Service, Department of Surgery, University of California, San Francisco, the authors report their experience since 1968 of 21 renal transplantations performed in 20 patients in terminal renal failure due to bilateral polycystic disease. Ages varied from 25 to 58 years, the average being 46·6 years. 11·5 years was the average time of diagnosis of the disease previous to operation and the average period of dialysis 13 months. 16 were cadaver grafts and 4 were from sibling donors. Cadaver kidneys were stored by hypothermic pulsatile perfusion. Patient were selected by tissue typing. 4 patients died, 2 with normal renal function 15 and 18 months after transplantation from reticulum cell sarcoma in brain and lung, and disseminated histoplasmosis respectively. 2 deaths occurred within 4 months of operation from secondary infection after treatment of rejection crises and the transplanted kidney had to be removed in two patients within 6 weeks for irreversible rejection episodes. 14 patients have excellently functioning grafts with serum creatinine less than 1·7 mg per 100 ml. The authors believe that a previous history of renal infection or significant haematuria necessitates bilateral nephrectomy before transplantation.

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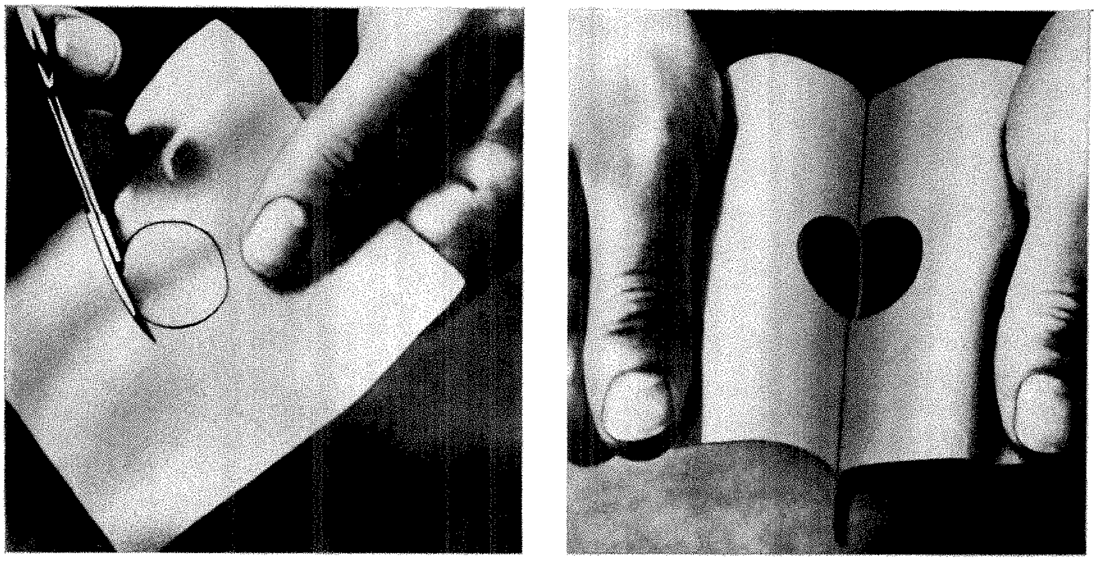

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THE TREATMENT AND CONTROL OF INFECTIOUS DISEASES IN MAN *by* **Pascal James Imperato**, *Dept. of Health, New York City.* Described in chapters are: historical aspects of infectious disease; medical sepsis and community and hospital management of this disease; and eighty infectious diseases, including contact management and specific treatment for each. *'74, 760 pp., 29 il., 20 tables, $34.50*

DIAGNOSTIC AND THERAPEUTIC AIDS IN UROLOGY *by* **Henry Bodner**, *Loma Linda Univ., Los Angeles, in collaboration with* **John S. Arconti, Jr., Allan H. Howard** *and* **Robert O. Pearman.** This book presents "tricks of the trade" in urology not found in standard textbooks. Oriented toward diagnosis, innovative uses and adaptation of equipment are included. *'74, about 349 pp. (6 3/4 x 9 3/4), 82 il., 5 tables*

A HANDBOOK OF URINALYSIS AND URINARY SEDIMENT *by* **Neil A. Kurtzman**, *Chicago, and* **Philip W. Rogers**, *Fort Sam Houston, Texas.* Common urinalysis techniques are described along with their interpretation and circumstances in which these techniques apply. Microscopic examination of urinary sediment is discussed with color illustrations of urinary elements. *'74, about 81 pp., 28 il. in full color, 2 tables*

ANAEROBIC DISEASES. *Edited by* **Albert Balows**, *U.S. Dept. of Health, Education, and Welfare, Atlanta, Georgia;* **Raymond Dehaan**, *Upjohn Company, Kalamazoo, Michigan;* **V. R. Dowell, Jr.**, *Center for Disease Control, Atlanta, Georgia; and* **Lucien B. Guze**, *UCLA, Los Angeles. (66 Contributors)* Bacteriology, clinical aspects, diagnosis and therapy of anaerobic bacterial infections are discussed. *'74, about 610 pp., 61 il., 121 tables*

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THE UROLOGICAL MANAGEMENT OF THE PATIENT FOLLOWING SPINAL CORD INJURY *by* **John W. Pearman** *and* **Ernest J. England**, *both of the Royal Perth Hospital, Perth, Western Australia. Foreword by* **G. M. Bedbrook.** Form and function of the normal urinary bladder is summarized. Conservative management is detailed which allows bladder emptying and freedom from urinary infection in spinal cord injury. *'73, 304 pp., 78 il., 22 tables, $15.50*

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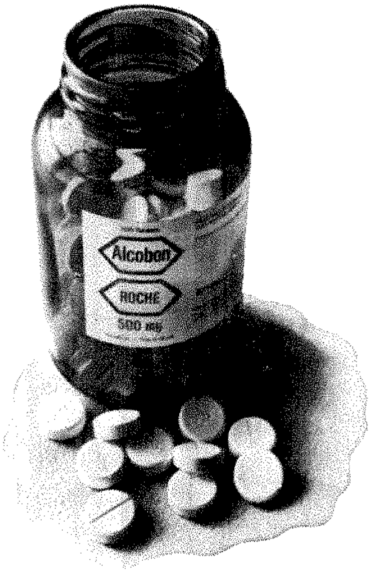

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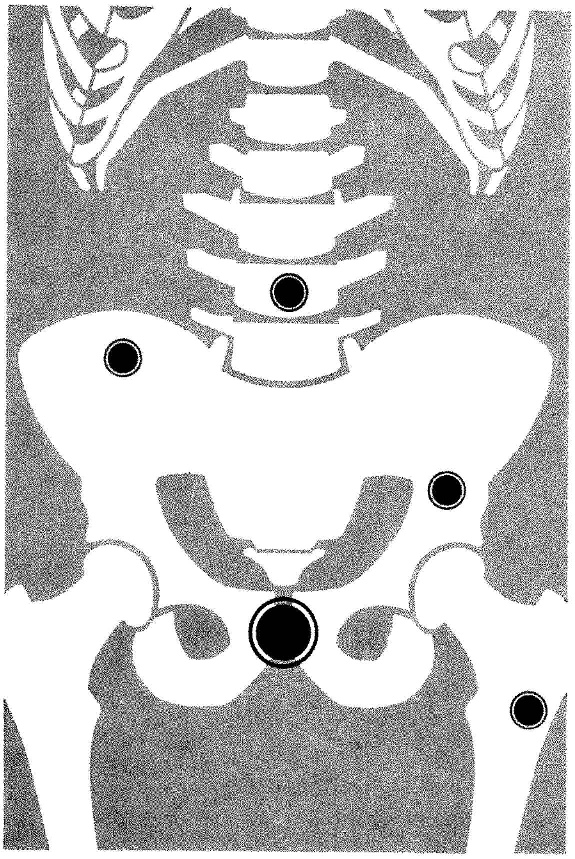

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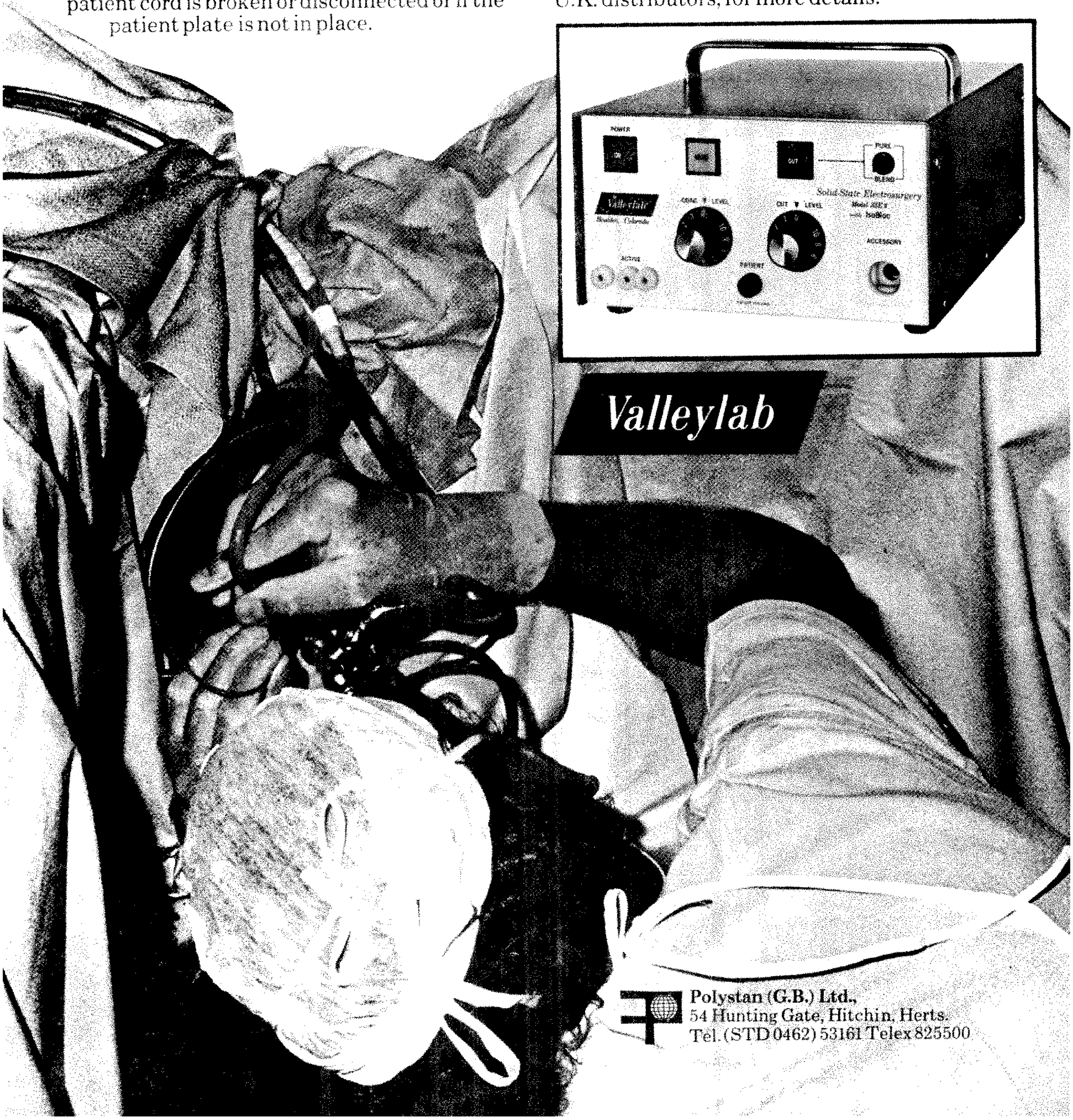

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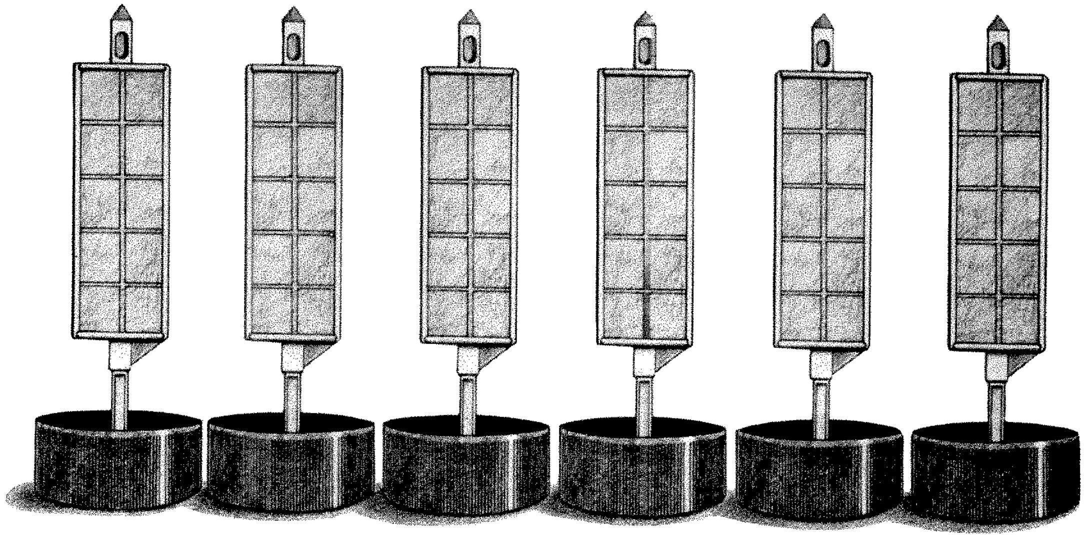

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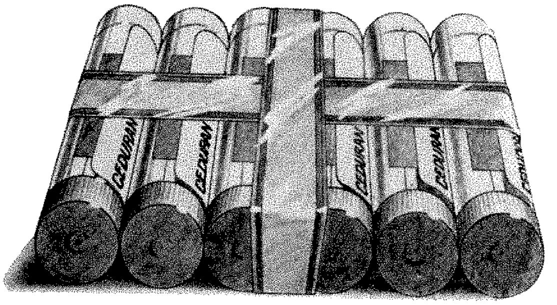

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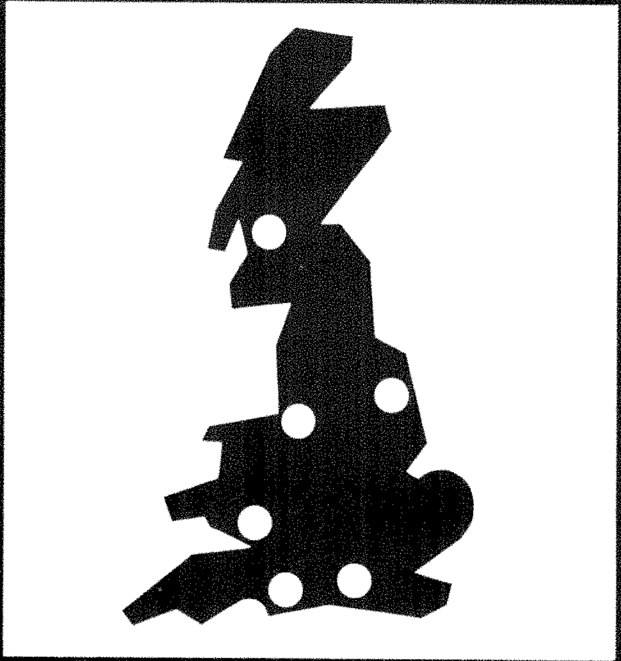
they've taken the country



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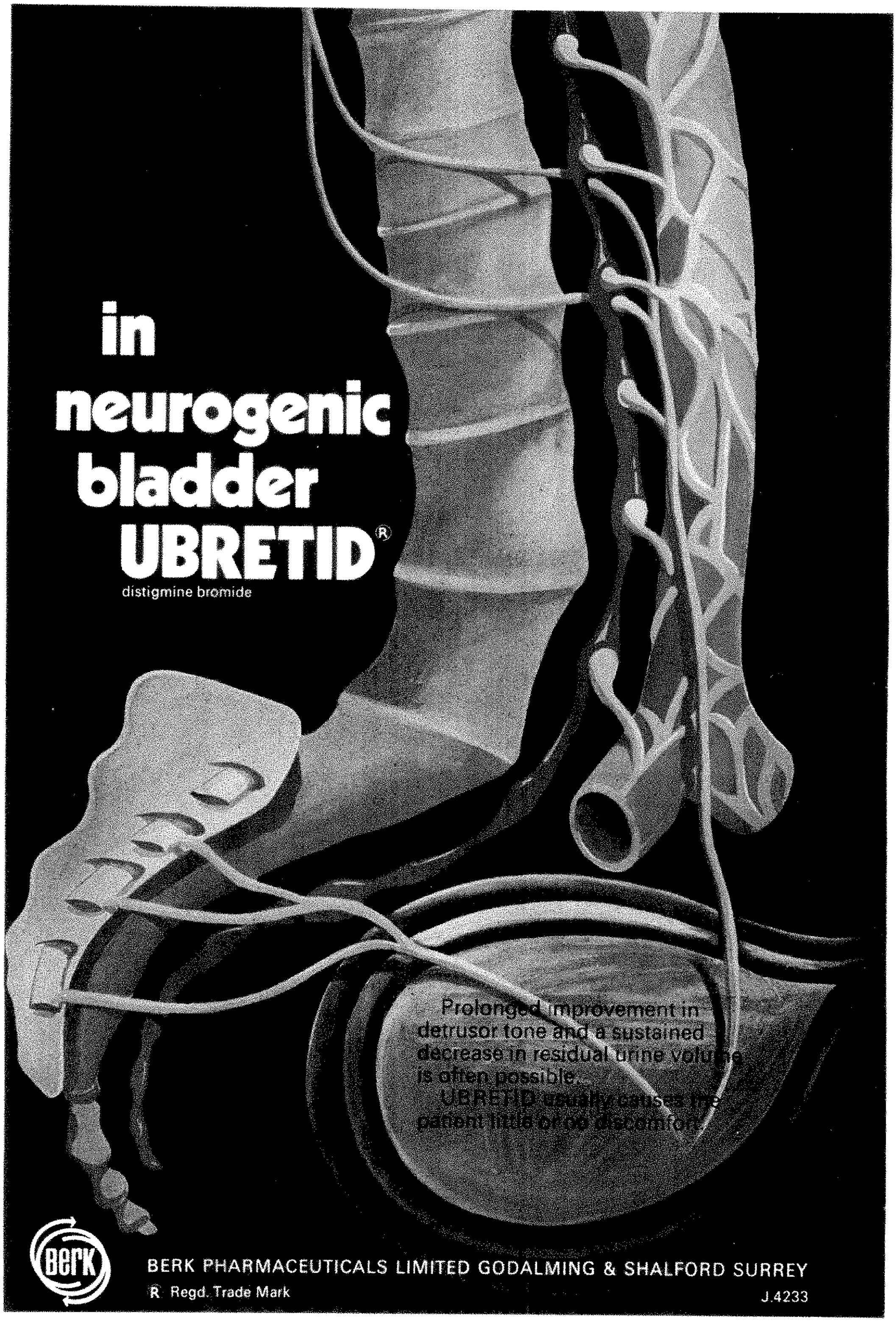

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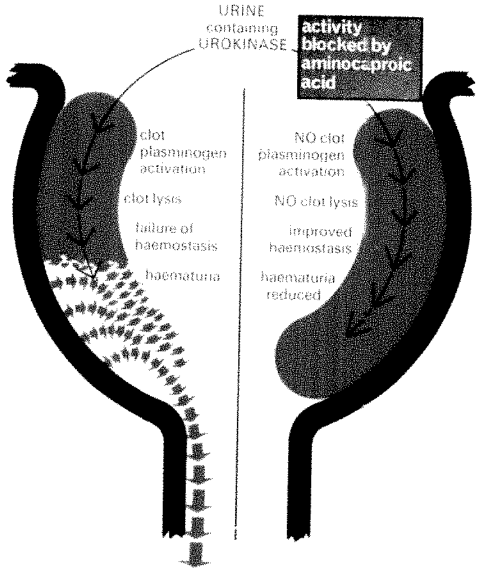

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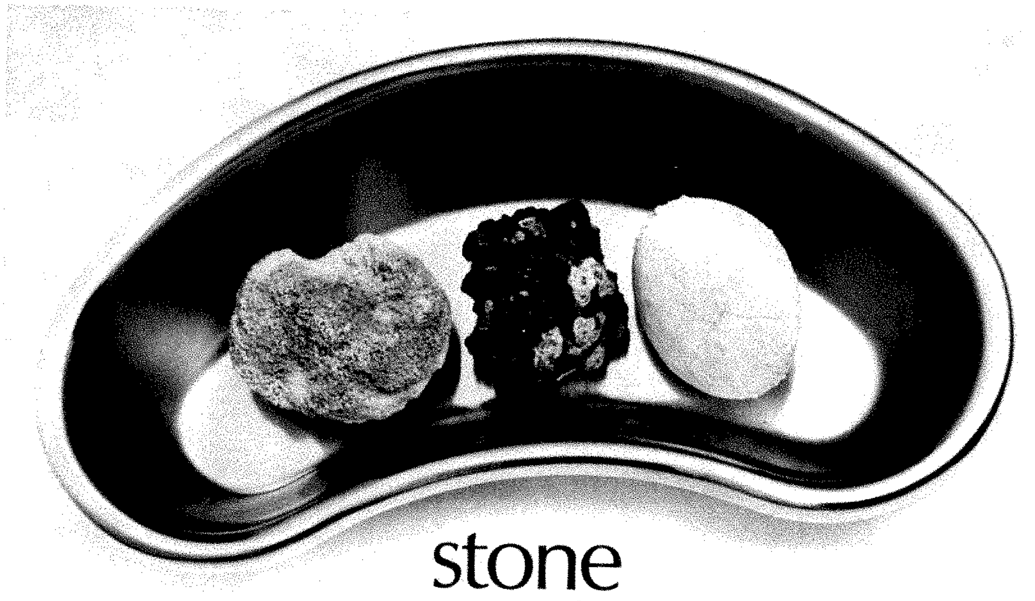

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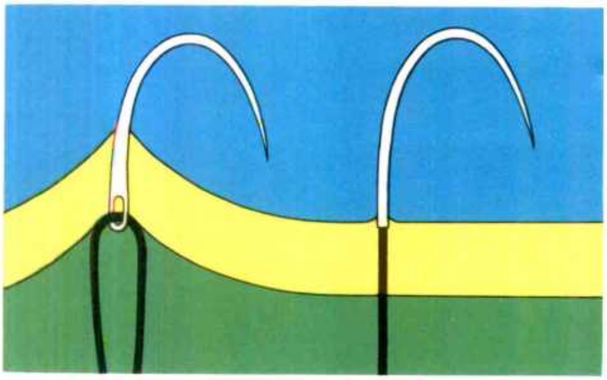

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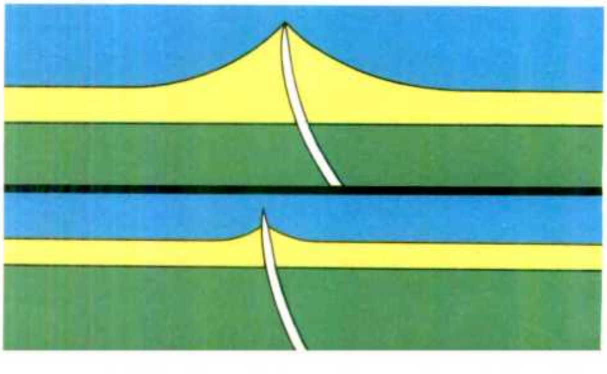

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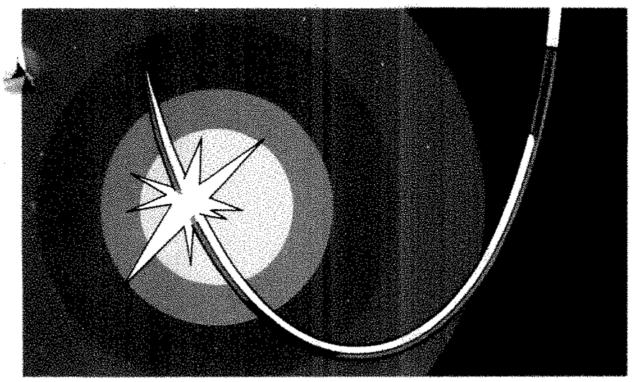

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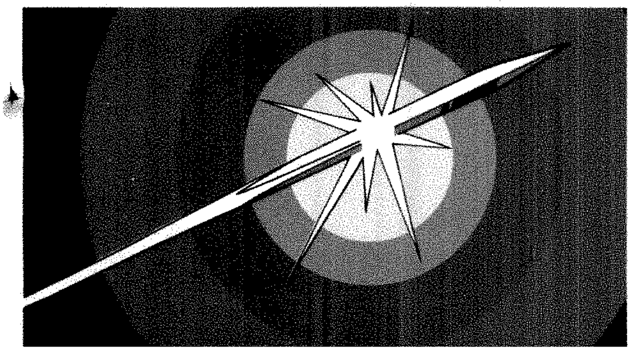

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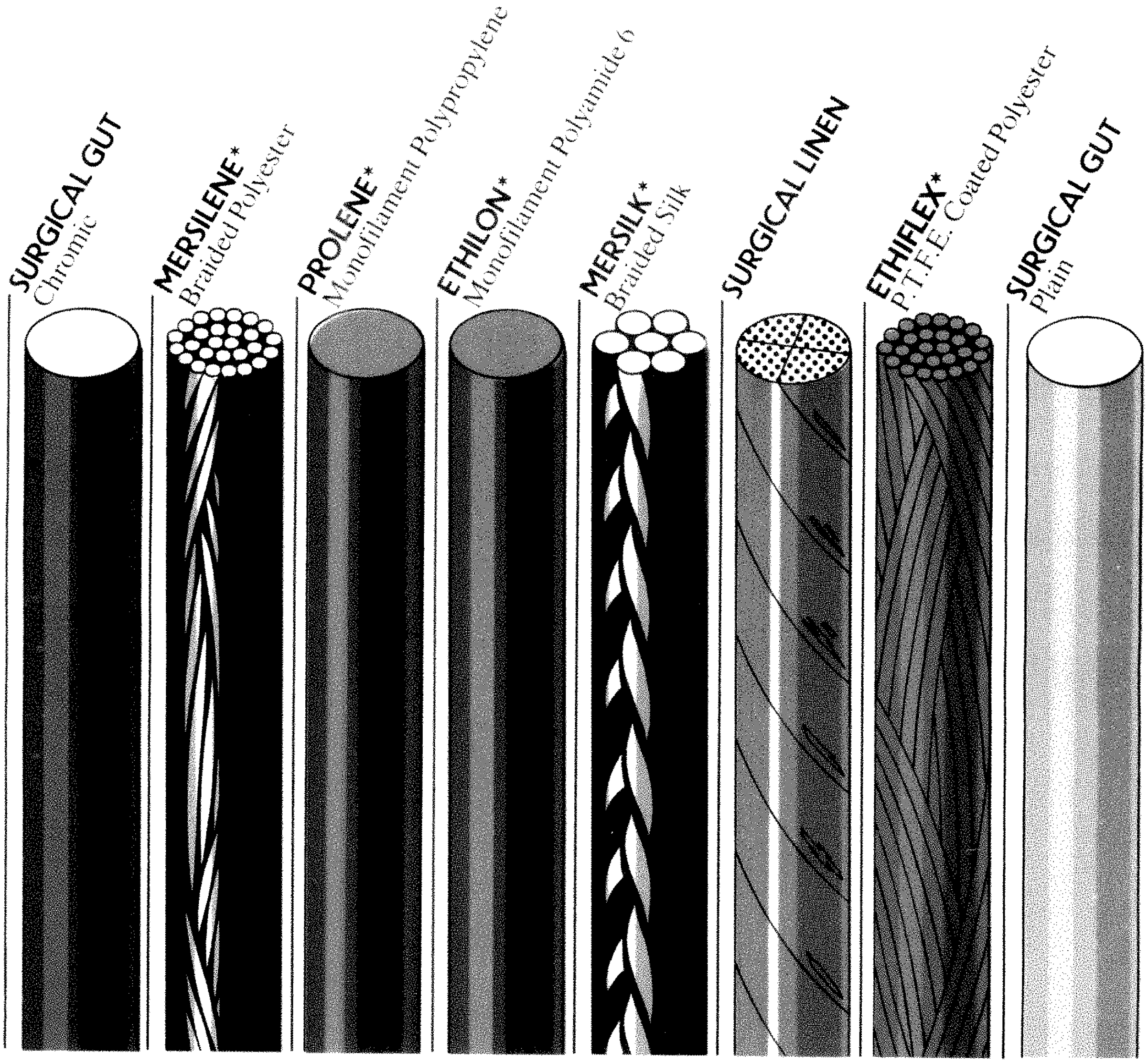
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More effective than ampicillin

There is evidence that Amoxil is more effective than ampicillin and this is particularly well illustrated in respiratory infections. Indeed, some reports have confirmed that Amoxil can succeed where ampicillin has failed[1,2,3]

Absorption unaffected by food

Early reports confirmed that Amoxil is twice as well absorbed as ampicillin, giving a peak serum concentration of 5.3 μg/ml[4] as opposed to ampicillin's 2.3 μg/ml[5]. Further work has shown that if both drugs are taken in the non-fasting state the overall absorption of Amoxil over the following 6 hour period is not significantly reduced, whereas that of ampicillin is reduced by nearly a third.

Amoxil's absorption characteristics mean that it is taken t.d.s. as opposed to ampicillin's q.d.s., and that the patient need not remember to take every dose in the fasting state.

Superior penetration

Studies at the Brompton Hospital[6] have shown that whereas ampicillin penetrates well into purulent sputum it penetrates very poorly into mucoid sputum. These workers have shown that Amoxil penetrates equally well into both purulent and mucoid sputum, and suggest that this may have far-reaching consequences in the treatment of respiratory infections.

Better tolerated

Although ampicillin is generally well tolerated, rashes and diarrhoea can be an irritating nuisance. A review of published literature indicates that Amoxil produces substantially less rash and diarrhoea than ampicillin.

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An ingenious series of experimental infections in mice has demonstrated that Amoxil exerts ". . . a more rapid bactericidal effect than ampicillin and this could be correlated with the difference in therapeutic effect."[7]

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References: (1) Brit. J. Dis. Chest., (1972), 66, 185. (2) S.A. med. J., (1973), 47, 717. (3) Chemotherapy, (1973), 18, (Suppl.), 19. (4) Brit. med. J., (1972), 3, 13. (5) Antimicrobial Agents and Chemotherapy (1970), 438. (6) To be published (7) Antimicrobial Agents and Chemotherapy, (1970), 416.

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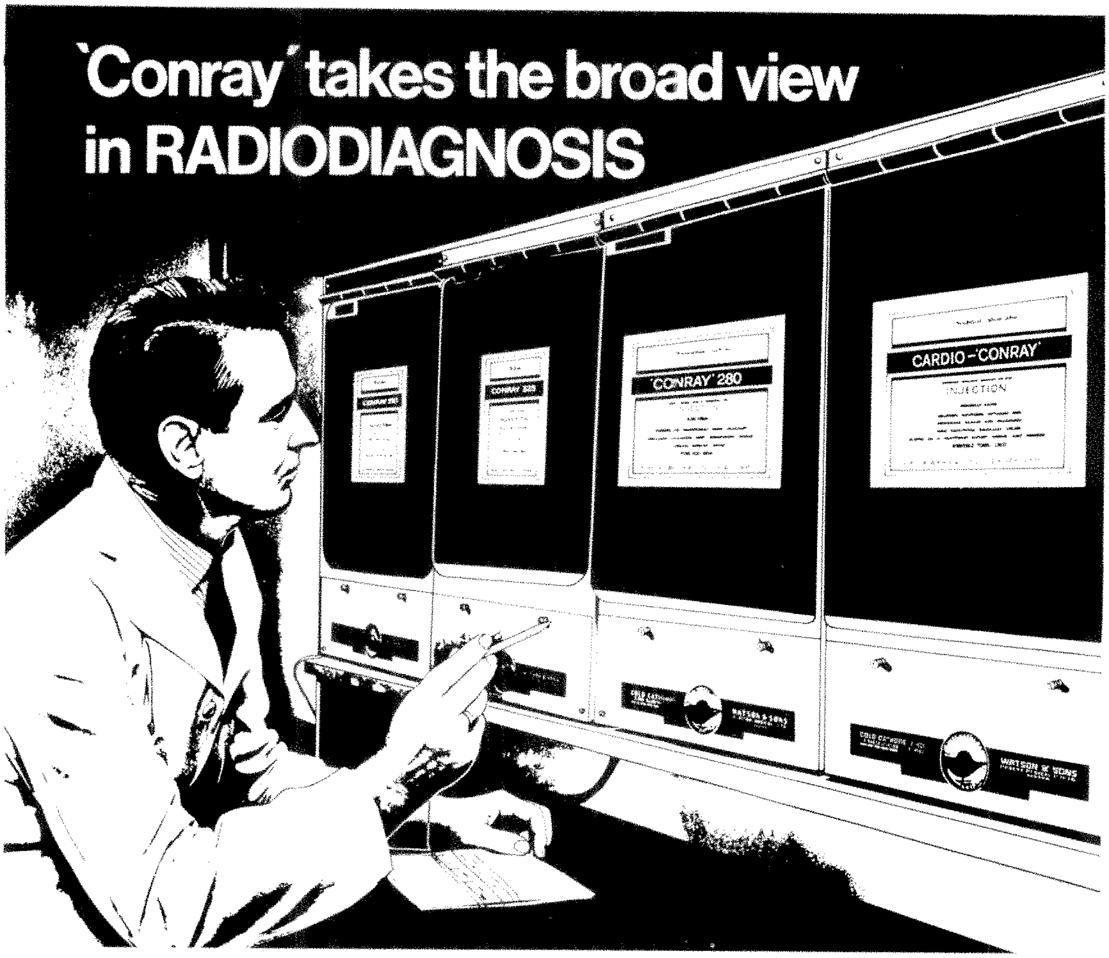

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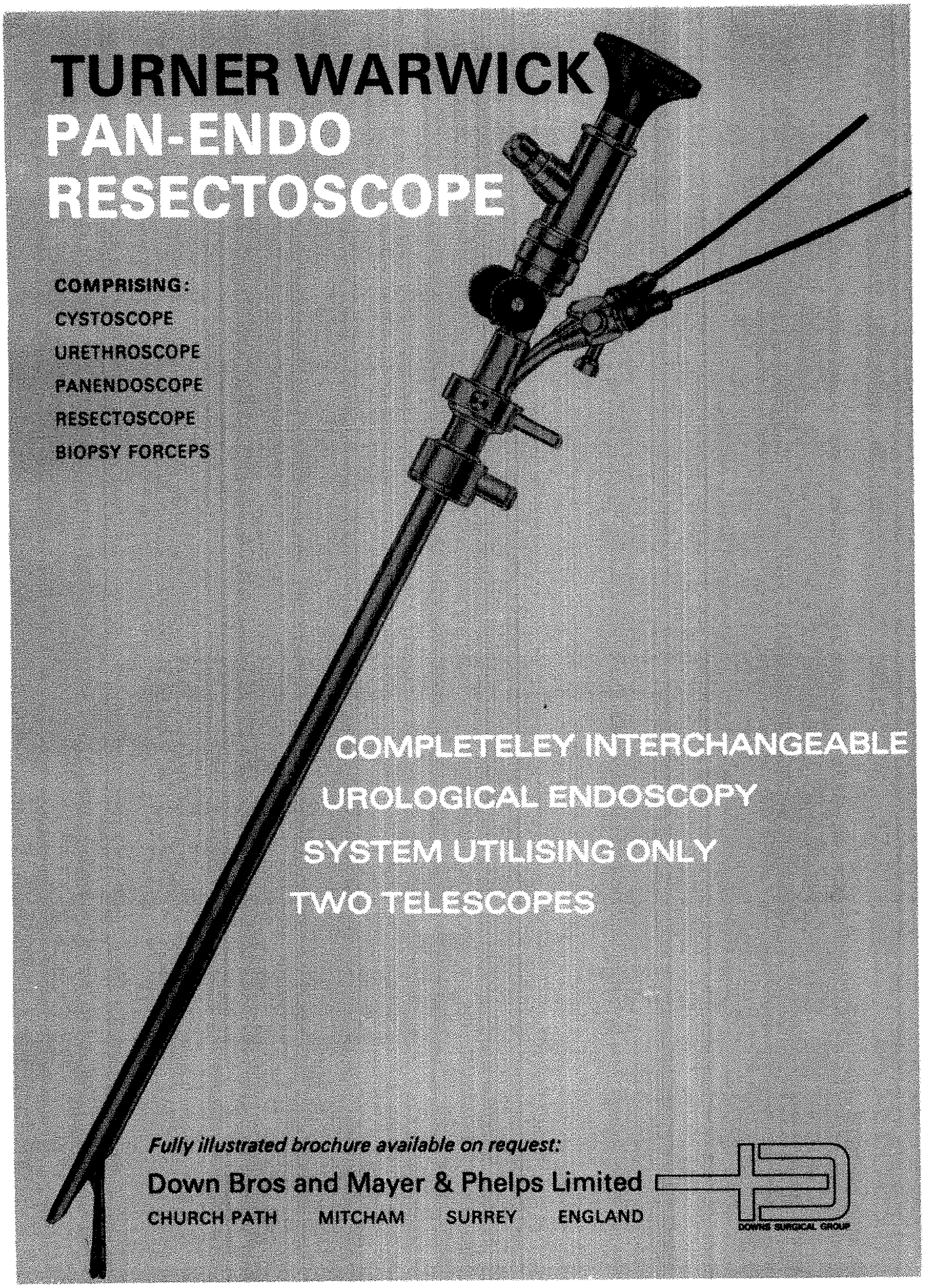

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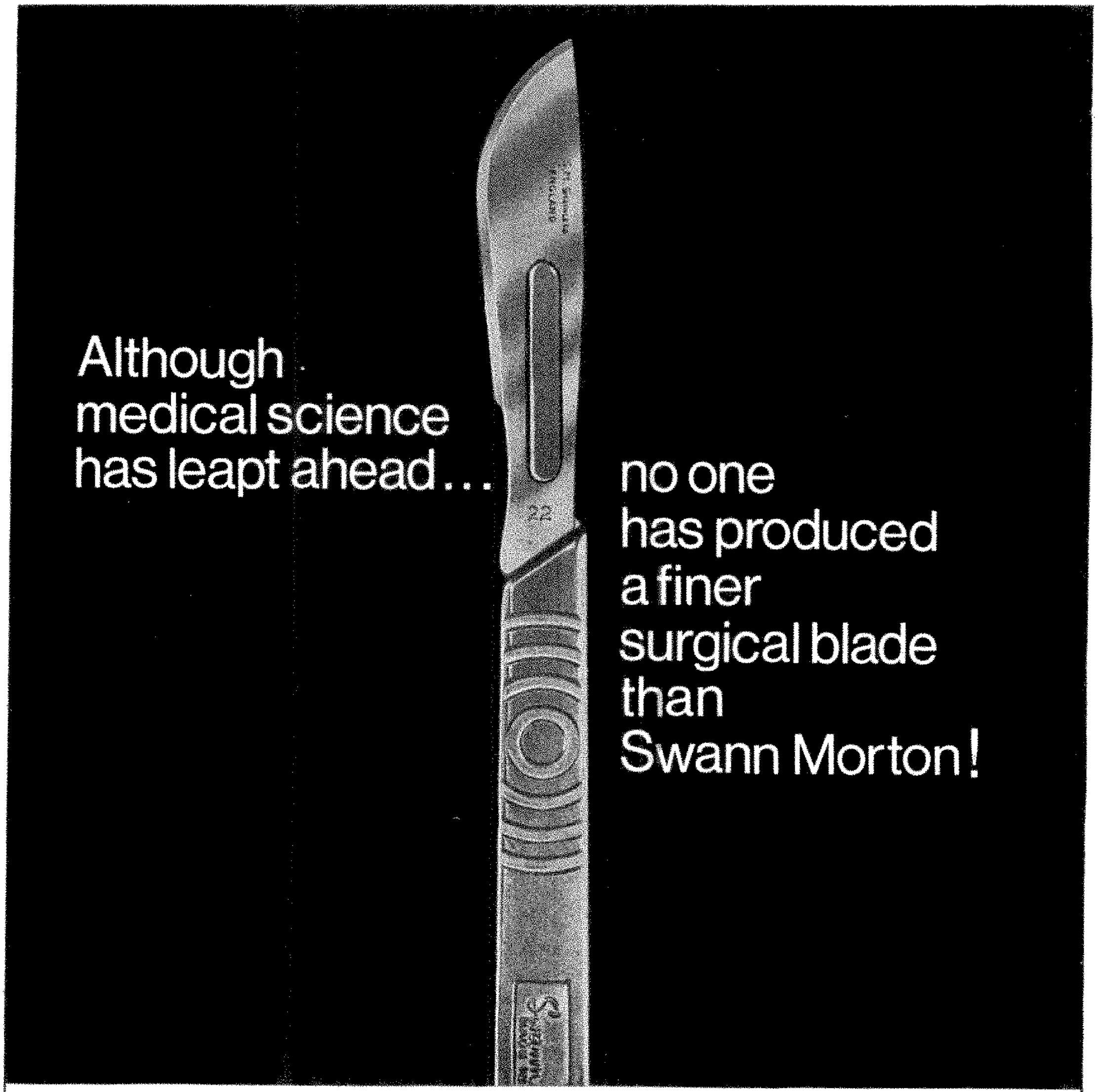

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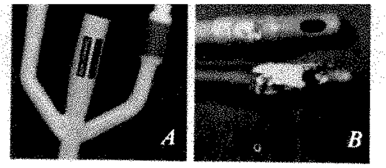

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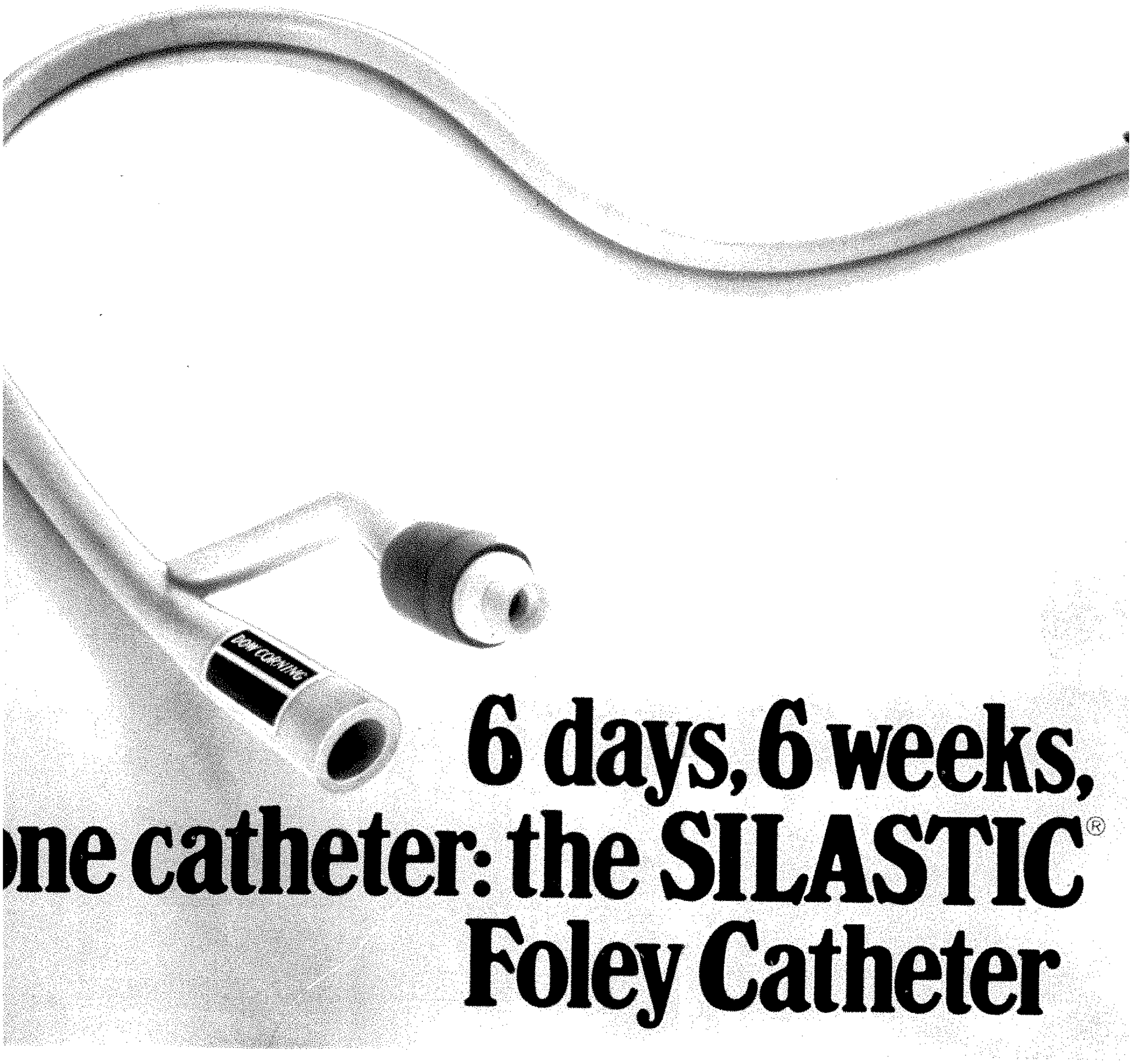

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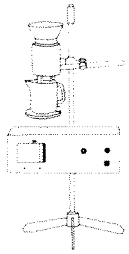

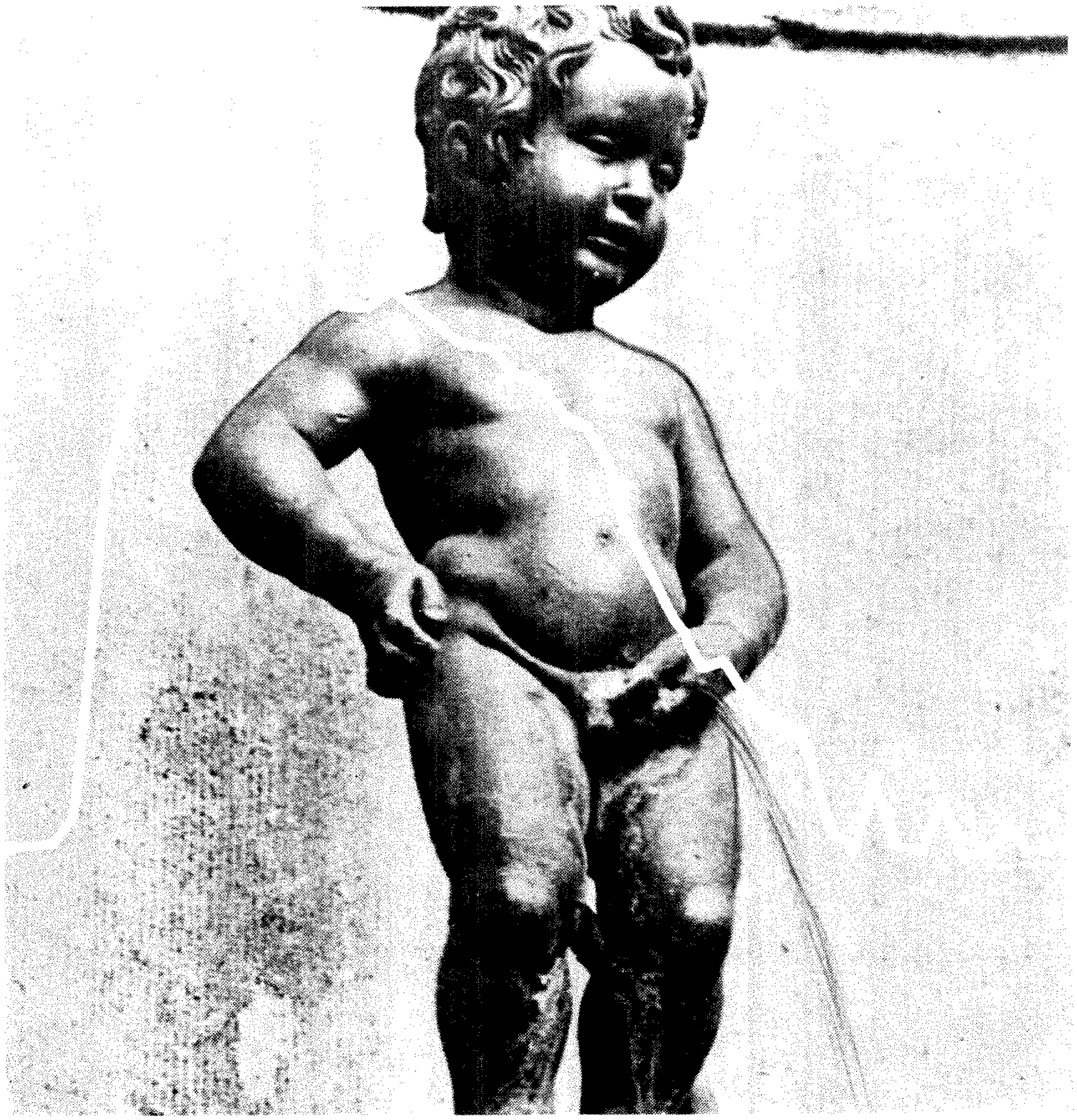

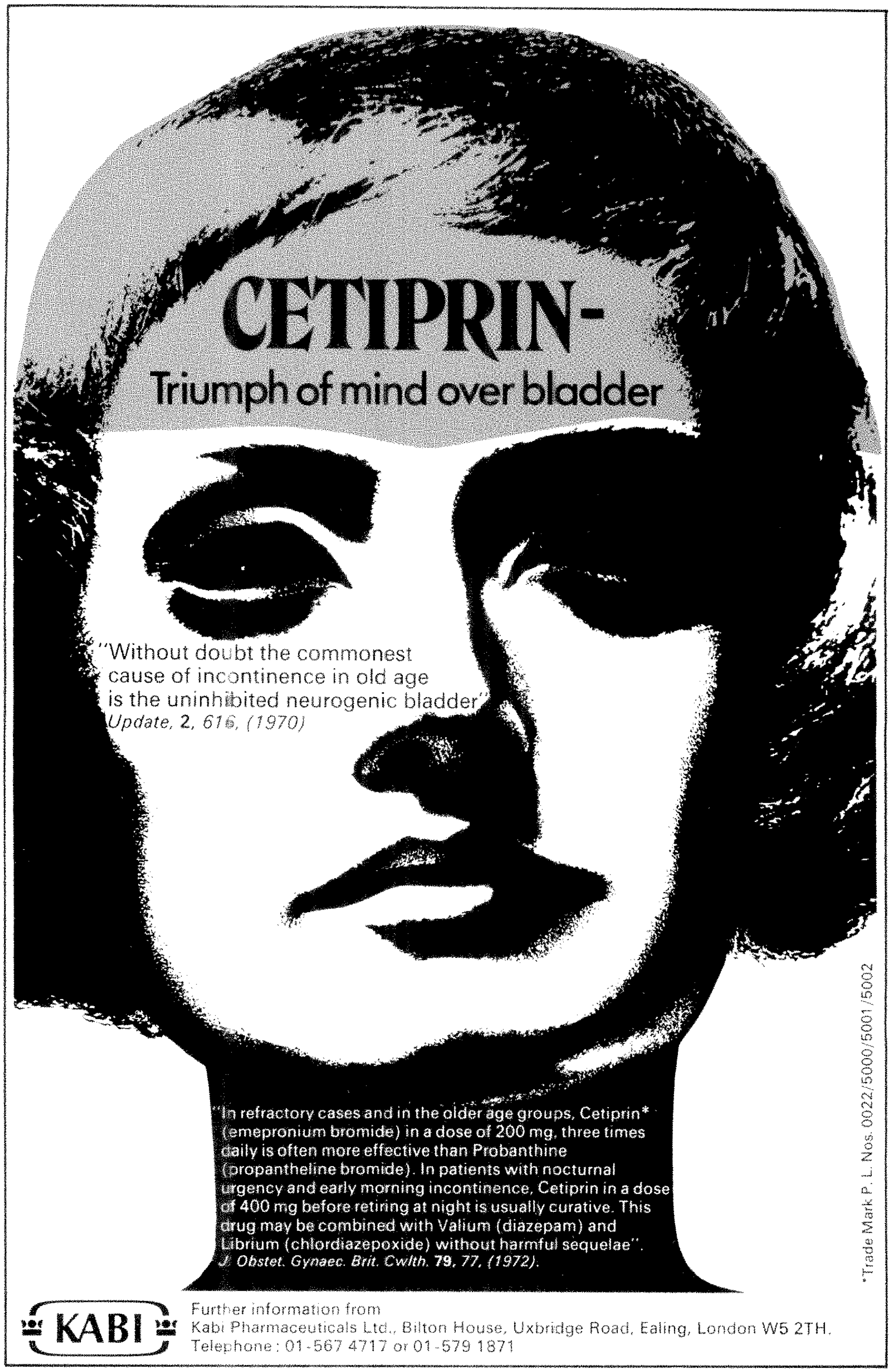

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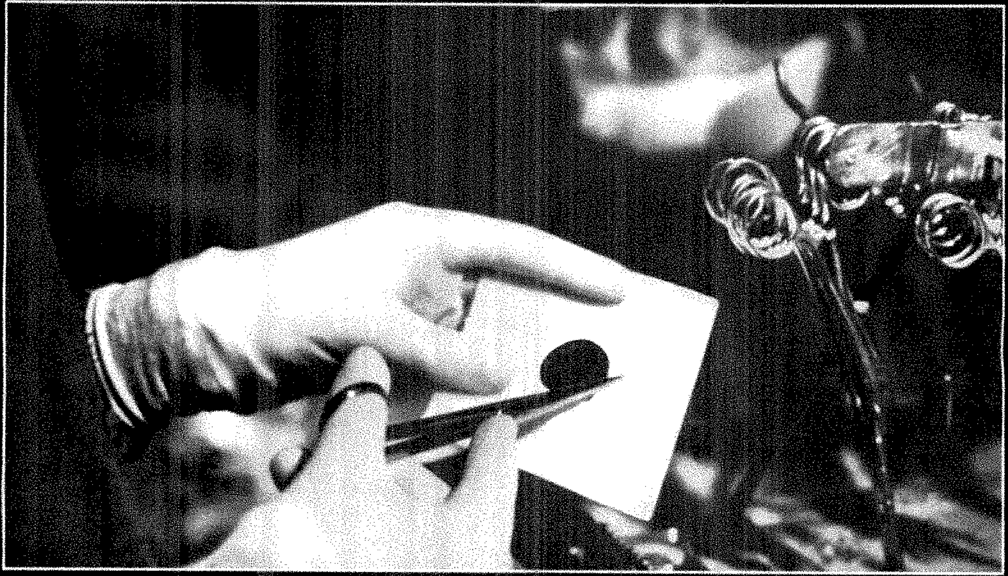

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Blood Background Subtraction Renography in Acute Renal Failure

S. LAVENDER and J. N. BROWN
Wessex Regional Renal Unit, St Mary's Hospital, Portsmouth

In the management of acute renal failure there is a need for an investigation to distinguish between acute intrinsic renal disease, obstructive uropathy and chronic renal disease. It has been claimed that radioactive renography can distinguish between these conditions (Winter, 1959; Trinkle and Kiser, 1964). Because of the simplicity of renography and the speed with which results can be obtained even in severely ill patients, it would seem to be very suitable.

However, Wax and MacDonald (1966) and Mayo and others (1971) have suggested that bilateral obstructive uropathy may give an identical renogram to that of acute intrinsic renal failure. Joekes and Rellan (1965) emphasised the asymmetry of the 2 kidney traces in the renogram of ureteric obstruction. Britton and Brown (1968) have advocated computer assisted blood background subtraction (C.A.B.B.S.) renography to eliminate interference by activity in the renal environment. Using this technique they confirm the distinction between the asymmetrical renogram of obstruction and the symmetrical tracings found in acute renal failure (Britton and Brown, 1971; Britton, Bluhm and Brown, 1971). All these reports have shown continuously rising tracings in acute renal failure and acute obstruction.

The following report demonstrates that total recovery from acute renal failure may be associated with the initial absence of any detectable uptake of hippuran by the kidneys. Where continuously rising tracings are obtained these may be asymmetrical.

Materials and Methods

Serial analogue C.A.B.B.S. renograms were performed on the 8 patients admitted to the Wessex Regional Renal Unit with acute intrinsic renal failure between September 1971 and April 1972.

Analogue C.A.B.B.S. renograms were obtained by the method described in detail by Britton and Brown (1968 and 1971) using a mobile apparatus with patients reclining and supine. The analogue subtraction system allowed the corrected renogram to be printed out immediately. The kidney detectors were placed according to the position of the kidneys seen on abdominal X-ray. The collimators used had 7 cm apertures and the skin crystal distance employed was 5 cm. The relative sensitivity of each detector was checked using a standard source before each investigation. Standard doses of radioactive substances were used throughout (5μCi ^{131}I labelled Human Serum Albumin and 15μCi ^{131}I labelled Hippuran).

Case 1

A 22-year-old man developed oliguric renal failure after taking an overdose of various drugs. C.A.B.B.S. renogram on admission (Fig. 1) showed no concentration of hippuran by either kidney and could not be distinguished from that of an anephric patient (Fig. 2). He was treated by peritoneal dialysis. After 2 days' oliguria the renogram showed continuously rising symmetrical activity over both kidneys. Renal biopsy showed normal glomeruli but widespread tubular damage, together with some interstitial cellular infiltration. He subsequently recovered normal renal function. Eight months later the renogram (Fig. 3) was normal.

Case 2

A 25-year-old drug addict took a multiple drug overdose. He developed oliguric renal failure requiring peritoneal dialysis. C.A.B.B.S. renogram (Fig. 4) showed minimal concentration of hippuran by either kidney. Bilateral

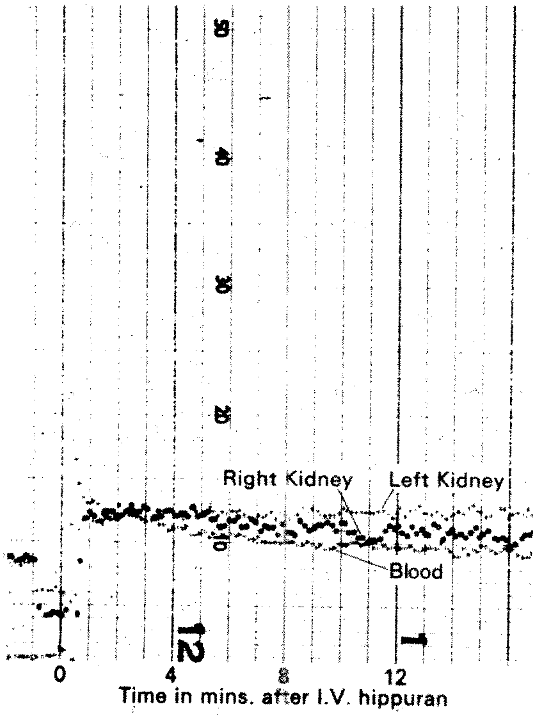

Fig. 1. Case 1. Acute renal failure following hypnotic overdosage. C.A.B.B.S. renogram on admission.

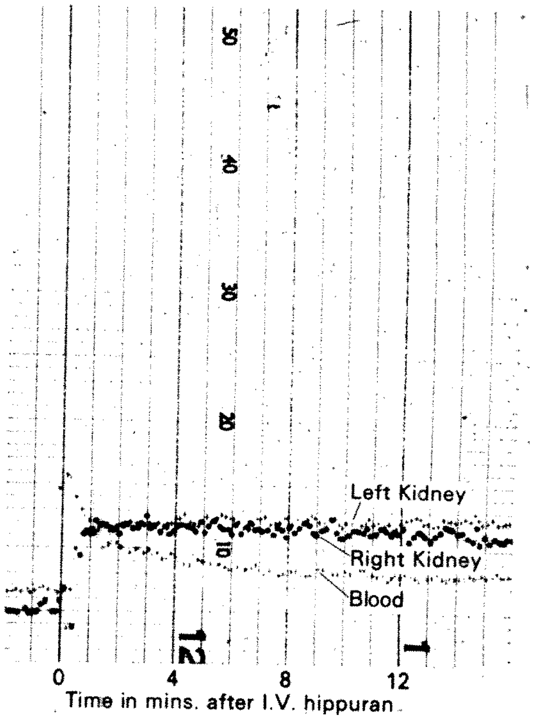

Fig. 2. C.A.B.B.S. renogram in an anephric patient.

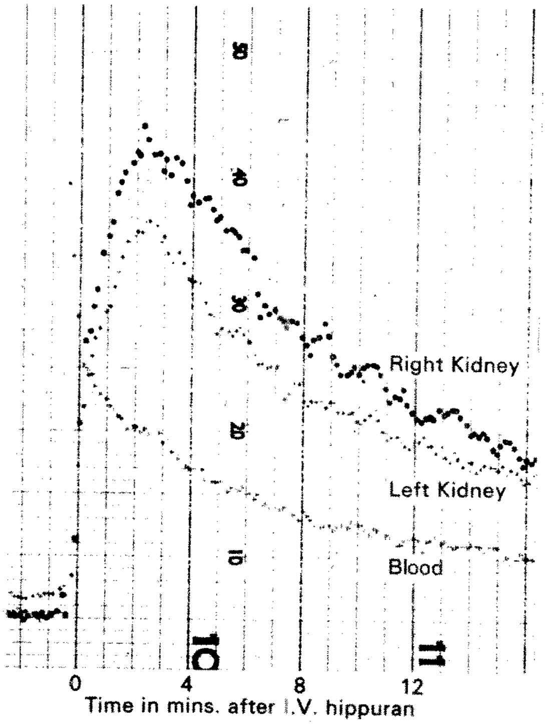

Fig. 3. Case 1. C.A.B.B.S. renogram 8 months after admission.

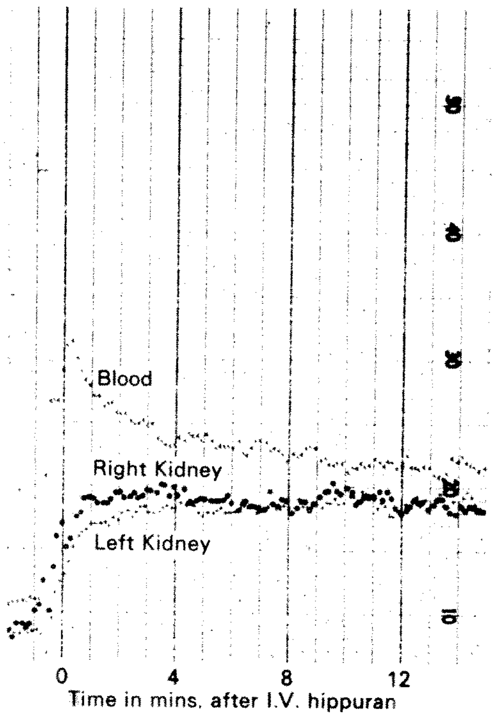

Fig. 4. Case 2. Acute renal failure following hypnotic overdosage. C.A.B.B.S. renogram on admission.

ureterograms showed normal-sized kidneys with no evidence of obstruction. Renal biopsy showed severe renal tubular damage with normal glomeruli. He developed clinical and histological evidence of focal ischaemic necrosis of muscle but myoglobin was not present in the urine. He recovered normal renal function. The renogram subsequently showed continuously rising symmetrical activity over both kidneys but returned to normal at 2 months.

Case 3

A 62-year-old woman developed acute renal failure following the administration of large doses of sulphadiazine for suspected bacterial meningitis. C.A.B.B.S. renogram showed grossly diminished symmetrical uptake of hippuran by both kidneys. Bilateral ureterograms were normal. After peritoneal dialysis she recovered normal renal function. Repeated renograms showed a return to the normal pattern over 1 month.

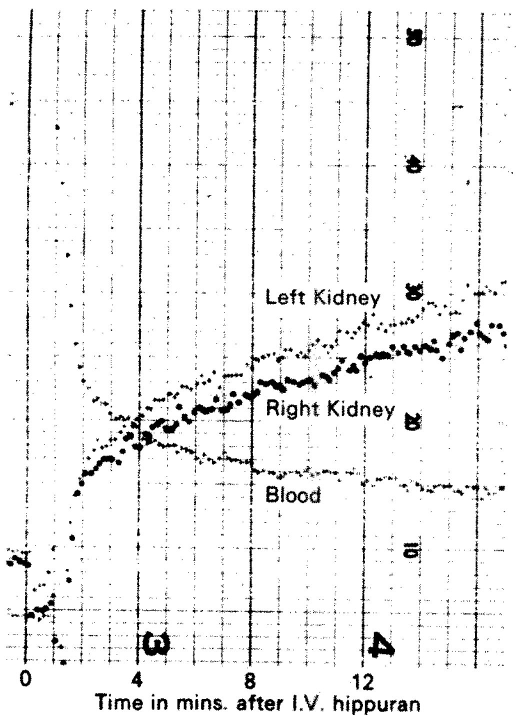

Fig. 5. Case 4. Acute renal failure with acute pancreatitis. C.A.B.B.S. renogram on admission.

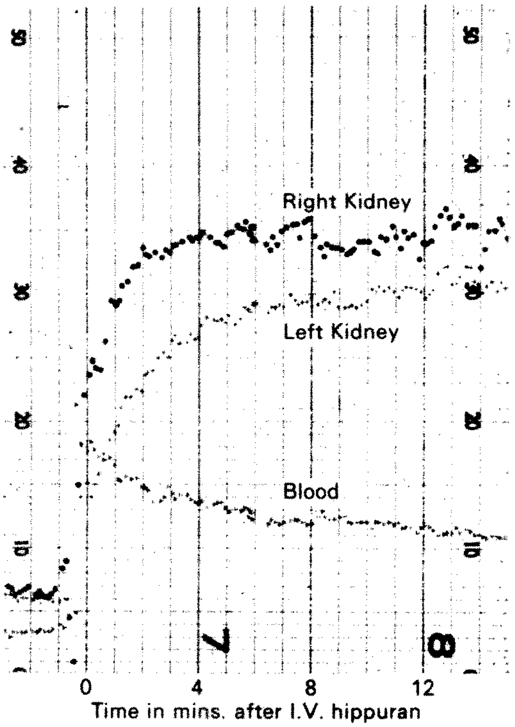

Fig. 6. Case 7. Acute renal failure following bronchopneumonia. C.A.B.B.S. renogram on admission.

Case 4

A 58-year-old woman was admitted with oliguric renal failure complicating acute pancreatitis. C.A.B.B.S. renogram (Fig. 5) showed symmetrical continuously rising activity over both kidneys. Cystoscopy and bilateral ureterograms were normal. Uraemia was controlled by peritoneal dialysis but she died as a result of gastro-intestinal haemorrhage. Autopsy showed necrosis of the pancreas and duodenum but the kidneys and ureters were macroscopically normal. Renal histology showed gross tubular damage.

Case 5

A 52-year-old woman with essential hypertension was admitted following a myocardial infarct. She developed acute renal failure in association with transient hypotension. A C.A.B.B.S. renogram showed symmetrically rising activity without a peak over either kidney. Six months previously she had been shown to have a normal intravenous pyelogram. A repeat high dose pyelogram showed no evidence of obstruction. Her renal function and renogram subsequently returned to normal.

Case 6

A 52-year-old woman developed acute renal failure as the result of fluid and electrolyte loss from a villous papilloma of the rectum. The tumour was removed. Subsequently C.A.B.B.S. renogram showed symmetrical tracings with normal second phases, delayed peaks, and grossly impaired third phases. She made a complete recovery and the renogram progressively returned to normal over 1 month.

Case 7

A 62-year-old man developed acute renal failure complicating bronchopneumonia. C.A.B.B.S. renogram (Fig. 6) showed asymmetrical rising second phases with no evidence of a peak. He was treated conservatively and made a full recovery. He regained normal renal function and a normal renogram.

Case 8

A 59-year-old woman with a history of manic depressive psychosis treated with lithium was admitted with lithium intoxication and acute renal failure. C.A.B.B.S. renogram showed asymmetrical continuously rising tracings over both kidneys. A renal biopsy showed severe tubular damage with minor glomerular abnormalities. She was treated with peritoneal dialysis and made a complete recovery. An intravenous pyelogram was normal. The renogram progressively returned to normal over 6 weeks. This case is reported in detail elsewhere (Lavender, Brown and Berrill, 1973*a*).

Discussion

In 1 of the 8 patients with acute renal failure reported above (Case 1) a C.A.B.B.S. renogram was obtained that was indistinguishable from that of an anephric patient. In 2 patients (Cases 2 and 3) the tracings were similar to those seen in advanced chronic renal failure. However, these 3 cases made a complete recovery. Three cases (4-6) showed symmetrical continuously rising tracings, but 2 cases (7, 8) had asymmetrical renograms which could have been interpreted as indicating obstruction. In no patient was there any evidence of obstructive uropathy.

Flat renograms obtained without background subtraction have been said to indicate a poor prognosis (Wax and MacDonald, 1966; Mayo *et al.*, 1971). However, Britton and Brown (1971) have shown that after blood background subtraction such renograms may reveal unsuspected urinary obstruction with some recoverable renal function. Recovery of normal renal function where a C.A.B.B.S. renogram has shown no uptake of hippuran has not previously been reported. The present report suggests that this can occur in acute intrinsic renal disease. It also suggests that some asymmetry of renograms in acute oliguria does not necessarily favour a diagnosis of obstructive uropathy. This is contrary to the reports of Joekes and Rellan (1965), Britton and Brown (1971) and Britton *et al.* (1971).

Little is known about physiological changes that occur within the nephron and its circulation in acute renal failure. It may be that the continuously rising renogram tracings seen in this condition are due to preservation of some active uptake of hippuran by the tubular cells associated with failure of transport into the tubular lumen. In the cases with relatively flat renograms which we report there must be failure of active uptake of hippuran by the tubular cells. It may be important that in these cases various drugs appeared to have been involved in producing acute renal failure. However, in the case precipitated by lithium continuously rising traces were obtained. In the 4 other cases showing active uptake of hippuran oliguria was precipitated by circulatory failure due to hypovolaemia, hypotension or septicaemia. Lavender *et al.* (1973*b*) have shown that the renogram obtained in the oliguric phase following renal transplantation shows accumulation of hippuran over the graft wherever normal function is eventually obtained. It may be that other forms of acute reversible renal failure due to disturbance of renal perfusion are associated with a relatively greater effect of hippuran transport from tubular cell to lumen than of uptake into the cell from blood.

Conclusions

Despite its simplicity the practical value of renography in the differential diagnosis of oliguric renal failure remains limited. Symmetrically rising traces probably indicate potentially reversible intrinsic renal disease, although acute obstruction affecting both sides equally cannot be excluded. Grossly asymmetrical rising traces are probably due to acute obstruction, but some asymmetry can occur in reversible intrinsic renal disease. Failure of hippuran concentration does not necessarily indicate chronic renal disease. It may occur in acute renal failure and be associated with complete recovery.

Summary

Serial computer assisted blood background subtraction renograms have been performed in 8 patients with acute renal failure.

One patient showed an initial tracing identical to that from a case with a bilateral nephrectomy; in 2 patients initial tracings were indistinguishable from those of cases of advanced chronic parenchymal renal disease; however all 3 patients made a complete recovery.

In 3 patients symmetrical continuously rising renograms were obtained as previously reported in acute renal failue.

In 2 patients asymmetrical renograms were obtained which could have been interpreted as indicating obstructive uropathy.

Renography in acute renal failure must be interpreted with extreme caution.

We are grateful to Professor A. Polak and Dr H. A. Lee for their advice.

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British Journal of Urology (1974), **46**, 253–256

Simple Renal Hypothermia

VILLIS MARSHALL and JOHN BLANDY
Department of Urology, The London Hospital, London

Although in the past we have hardly ever found it necessary to use hypothermia as an adjunct to the Gil-Vernet operation for even large renal calculi, there are times when it can be helpful, especially when a small fragment is left behind in an outlying calyx, or when a large mushroom extension of the main stone has to be removed through a thick layer of overlying parenchyma. Hypothermia may also be useful during partial nephrectomy and renal arterial surgery.

As a means of prolonging the safe period of renal ischaemia, hypothermia has been used for a number of years (Stewart, 1960; Graves, 1963). Generally surgeons have cooled the kidney with ice slush, but it is tedious to prepare slush which is both sterile and has the right consistency, and as with surface cooling coils (Wickham, Hanley and Joekes, 1967; Hanley, 1970), there is a possibility that tissue in direct contact with ice or coil may become frostbitten. We have perfused Gelin's fluid through the renal artery during certain exceptional operations on renal arterial aneurysms, but this is too complicated a method for routine use (Eadie *et al.*, 1965; Hardy *et al.*, 1973).

We now describe a very simple method which uses only standard equipment available in any operating theatre, yet is capable of producing renal hypothermia when desired. From our experience of a small pilot series, we feel we can recommend this technique to surgeons who are likely to use hypothermia so seldom as to make it uneconomical to purchase expensive cooling machinery, and who may be unable to ensure that sterile ice slush is available at short notice.

Method

Normal saline in flasks or plastic packs is led through an ordinary transfusion set to a blood-warming coil immersed in a bowl of unsterile ice-salt slush, and thence via 1 or 2 sterile extension tubes to the kidney (Fig. 1). Renal temperature is measured with a thermocouple.

At operation, the kidney is isolated, its artery taped, and a split plastic sheet arranged around the kidney so as to form a well (Fig. 2) into which the cold saline is run. The saline issues from the cooling coil at 6° to 7°C if the flasks have been previously stored in the main compartment (4°C) of a refrigerator overnight. If pre-cooled saline is not available and the saline enters the cooling coil at room temperature, it emerges at about 14°C. With pre-cooled saline, the temperature of the kidney will fall to 20°C within about 10 minutes.

When a staghorn calculus is to be removed, we proceed with the Gil-Vernet operation in the usual way, exposing the renal pelvis and removing as much as we can of the stone through the extended pyelolithotomy (Blandy and Tresidder, 1967). If the need then arises to cool the kidney, the cooling system is rapidly set up, the renal artery is occluded, and the cold saline is run into the renal pelvis.

The temperature falls more rapidly with this combination of intrapelvic and surface cooling than when surface cooling is used alone.

Cooling is stopped when the thermocouple records a temperature of 22°C, 2 cm below the surface of the kidney: further cooling continues to take place to 20°C over the next few minutes.

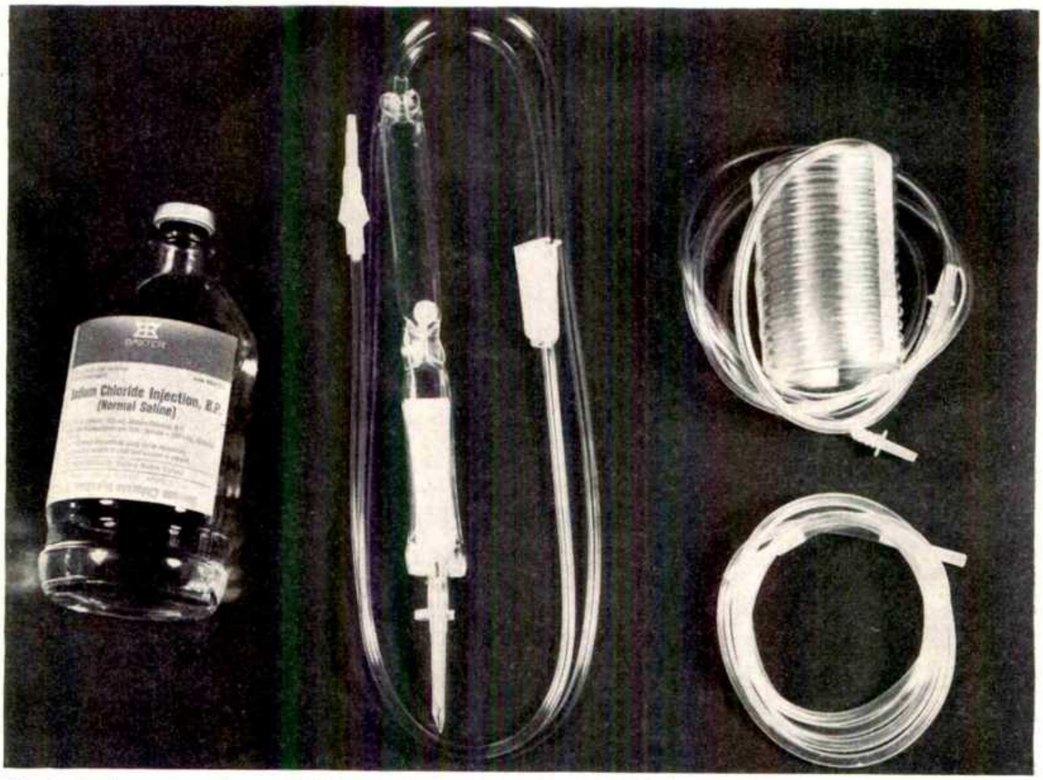

Fig. 1. Equipment used to cool kidneys—flask of normal saline, infusion set, blood-warming coil and sterile extension piece.

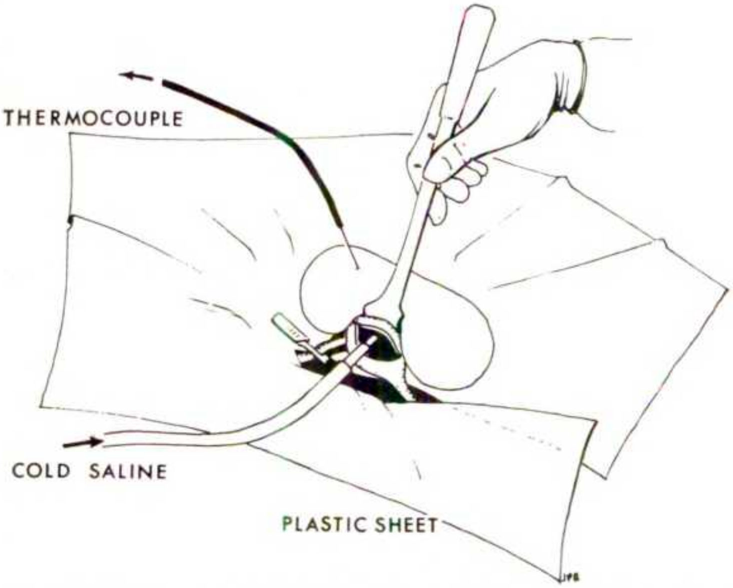

Fig. 2. Renal artery occluded and kidney surrounded by plastic sheet immediately prior to cooling.

Results

We have used the method in a small pilot series of 7 patients (9 kidneys)—1 had a partial nephrectomy, 5 had an extended pyelolithotomy (2 patients had bilateral calculi) and 1 had an intra-renal foreign body.

The mean time to achieve cooling to 20°C was 9·5 minutes: the shortest was 7·5 minutes; the longest 13 minutes. The longest period of ischaemia was 55 minutes: the mean ischaemic time was 42 minutes. There were no complications which can be put down to hypothermia. There was no undue postoperative ileus. Postoperative urograms were either unchanged or improved. When the other kidney was normal, the blood urea and creatinine were unchanged. In the patient with bilateral stones (Fig. 3), both kidneys were cooled at successive operations. Before the first operation the blood urea was 71 mg % and the creatinine clearance 42 ml/min. Two weeks after the second operation, the urea was 55 mg % and the creatinine clearance 68 ml/min.

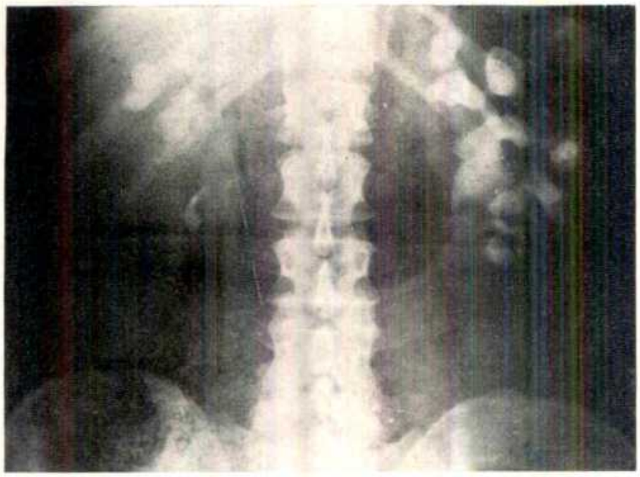

Fig. 3. X-ray showing bilateral staghorn calculi. Peripheral fragments were removed after cooling.

Discussion

This very simple technique uses the standard equipment which is to be found in any operating room. It is best if saline has been put in the refrigerator overnight before the operating list to cool it to 4°C, but the use of the coil makes it perfectly possible to carry out adequate cooling even if the saline starts off at room temperature.

There is always a lag of 2 to 3 minutes before the temperature begins to fall: thereafter the rate of fall is quite rapid—about 2 to 3 centigrade degrees per minute. If it does not fall after the first 3 minutes, one should suspect that a polar vessel has not been occluded by the clamp. This occurred in the case which took 13 minutes to cool down.

In calculus surgery it is likely that hypothermia will be needed for very difficult and crumbly calculi and in these cases the tiny fragments can only be adequately removed by vigorous irrigation; thus the initial presence of the cooling saline will make little difference to the wetness of the field or the adequacy of exposure.

How cool does the kidney need to be in order to be protected from the effects of ischaemia? The studies of Wickham *et al.* (1967) showed that there was a fairly wide range of temperature over which the protective effect was much the same: so that precise control of cooling is not necessary, nor does the kidney have to be made very cold. Indeed, cooling to 0°C has been shown to be deleterious (Wickham *et al.*, 1967).

We do not think that surgeons need to use hypothermia very often in renal surgery, but it would be a pity if they failed to use it because they thought it required special equipment. Thermocouple, blood-warming coils, drip sets, extension tubing, and unsterile ice and salt are available in every hospital. With this and a sterile waterproof sheet, it is perfectly possible to produce hypothermia at short notice with minimal fuss and expense.

Summary

A blood-warming coil immersed in ice-slush rapidly lowers the temperature of normal saline and allows it to be used to cool a kidney to the range of hypothermia which protects it from the effects of ischaemia. This simple method of hypothermia has been shown to be effective in operations on 9 kidneys.

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Recurrent Mesenteric Venous Thrombosis Complicating Renal Transplantation

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Renal transplantation may be followed by a variety of complications. Usually these can be attributed to the side-effects of immunosuppressive drugs but on occasions the aetiology may be more obscure. Gangrene of the ileum and colon has recently been observed in a few patients (Powis *et al.*, 1972) and mesenteric arterial thrombosis has been proposed as the probable cause. We have encountered a further case of intestinal gangrene, but in this instance the cause was clearly thrombosis of the mesenteric veins. Since we have found no similar reports in the medical literature, we give here a brief description of this case.

Case Report

The patient was a 45-year-old woman who had suffered from chronic pyelonephritis for many years. Haemodialysis was instituted in October 1969 and was uneventful apart from recurring episodes of thrombosis in her arteriovenous shunts. In May 1971 a shunt was inserted into the vessels of her left groin and 1 week later a cadaveric kidney became available and transplantation was performed. After 14 days of oliguria, urine output increased, and her blood urea and serum creatinine fell to 52 mg % and 1·0 mg % respectively.

One month after transplantation the groin shunt clotted spontaneously, and shortly afterwards the patient developed an ilio-femoral venous thrombosis on the same side. Thrombectomy was performed and the shunt removed. Anticoagulation was instituted and was continued until November 1971 when it was gradually withdrawn. In December 1971 a routine renal biopsy was performed which showed very minimal changes of rejection. Coagulation studies performed at this time were normal.

On 8th February 1972, some 9 months after transplantation, the patient was admitted with severe abdominal pain and vomiting. Her abdomen was distended and very tender. She was currently taking 75 mg of azathioprine and 20 mg of prednisone. Laboratory tests gave the following results:

Hb. 13·8 g %: White count 26000/cu. mm.
Platelets 38,000/cu. mm: Serum sodium 139 mEq/l.
Potassium 3·6 mEq/l: Urea 86 mg %.
Creatinine 2·2 mg %: Serum amylase 210 I.U./l.
Liver function tests normal and X-ray of her abdomen showed dilated loops of small bowel.

Laparotomy was performed soon after admission and approximately 6 feet of ileum were found to be discoloured, of which 2 feet were completely gangrenous. There were no pulsations palpable in the mesentery of the affected bowel and the veins were noted to be distended with clot. The affected bowel was excised and an end-to-end anastomosis performed.

On the second postoperative day she again developed abdominal pain and distension. The results of further laboratory tests were as follows:

Hb. 14·1 g %: White count 16,400/cu. mm.
Platelets 30,000/cu. mm: Blood urea 144 mg %.
Serum creatinine 2·8 mg %: Serum amylase 284 I.U./l.
Clotting factors were normal and there was no evidence of fibrinolysis.

At re-exploration a further 3 feet of small bowel were found to be gangrenous (Fig. 1), although the bowel in the vicinity of the previous anastomosis was healthy. The mesentery, which was oedematous, contained many thrombosed veins although the mesenteric arteries were pulsating strongly. On this occasion, a principal mesenteric vein was opened and clot was extracted with a Fogarty catheter. Unfortunately this did not improve the venous

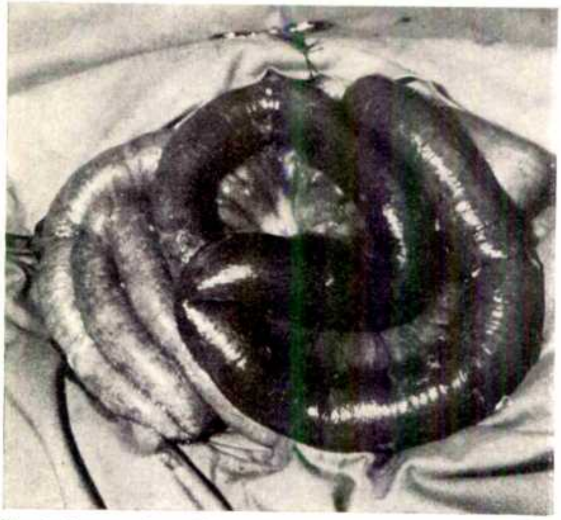

Fig. 1. Loops of small bowel as they appeared at the second operation. The intestine is engorged and prominent mesenteric veins are visible in the mesentery.

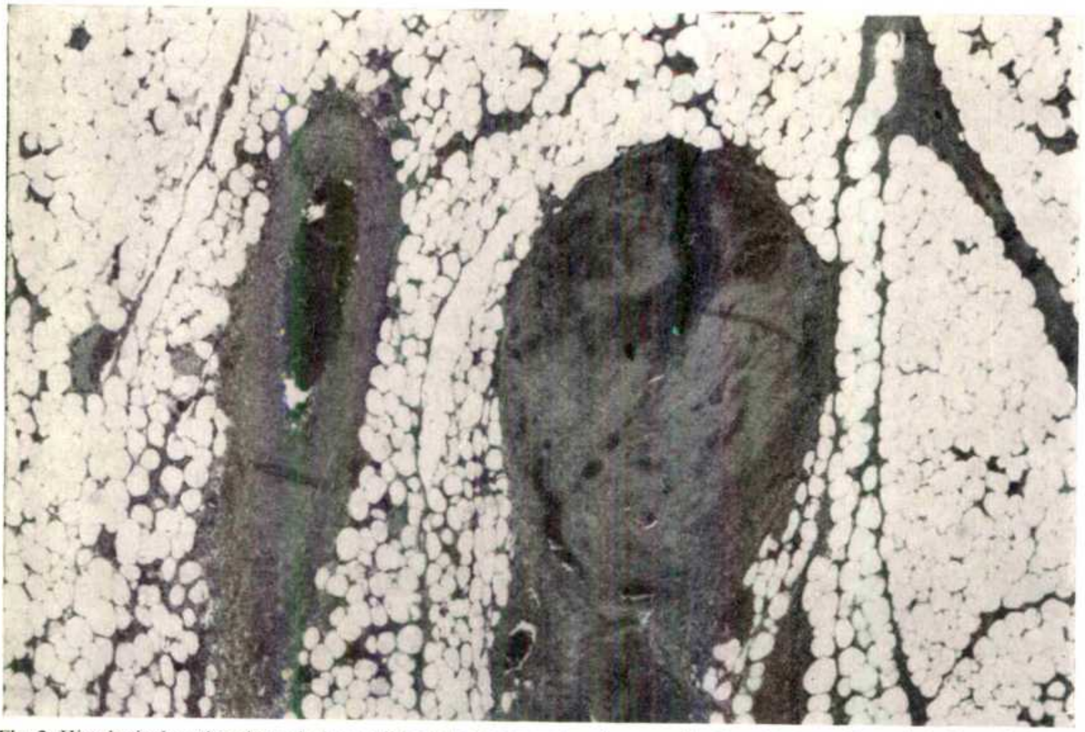

Fig. 2. Histological section through the small bowel mesentery showing a small vein and artery. The vein is distended with thrombus which is partly organised. The artery contains a conglomeration of red cells, but no fibrin. (Haematoxylin and eosin. ×40.)

drainage from the affected segment and a further 3 feet of bowel had to be excised, leaving just 4 feet of small intestine remaining. Anticoagulation was commenced postoperatively and Rheomacrodex was administered intravenously for 4 days. Although her initial progress was good, she later deteriorated and copious quantities of fluid were discharged from her wound. She became jaundiced and ultimately faecal material appeared in the drainage fluid. She died 13 days after her admission.

At postmortem, free red-coloured fluid was found within the abdominal cavity and one of the small bowel anastomoses was seen to be leaking. The remaining small and large bowel was plum coloured and partially necrotic. The mesenteric veins were thrombosed and thrombus was also found within the portal and splenic veins. The liver was shrunken and yellow. The transplanted kidney had small areas of haemorrhage in the cortex, but was otherwise normal on macroscopic examination and its vessels were free of thrombus. The patient's own kidneys were shrunken and their surfaces were granular. On histological examination the small bowel was seen to be necrotic and thrombus was present in the veins but not the arteries (Fig. 2). Although the liver had undergone autolysis some centrilobular congestion was apparent in most areas. The transplanted kidney exhibited the changes of chronic rejection, with fibrointimal thickening of arterioles and swelling of the interstitium and infiltration with mononuclear cells.

Discussion

Thrombosis of the mesenteric veins has been described in association with a number of conditions (Johnson and Baggenstoss, 1949). It may follow injury to the mesentery, as can occur with a volvulvus or intussusception, and can complicate cases of heart failure, thrombo-phlebitis, peritonitis, portal hypertension, polycythaemia and disseminated malignancy. It may also occur in women taking oral contraceptives (Miller, 1971). In 1935 Warren and Eberhard drew attention to the fact that approximately 50% of cases of mesenteric venous thrombosis arise quite spontaneously in the absence of any predisposing factor. Such an occurrence has been labelled "primary mesenteric venous thrombosis" and a large number of these cases has now been recorded (Berry and Bougas, 1950; Bussey, 1955; Naitov and Weismann, 1965; Mathews and White, 1971; Van Way, Brockman and Rosenfeld, 1971).

It would appear that the disease in our patient was of the "primary" type, since she had not been suffering from any of the conditions listed above. It is possible, however, that a hypercoagulable state may have existed prior to renal transplantation, as her facility to clot an arteriovenous shunt was all too evident at this time. There is no evidence that this state persisted after transplantation, and coagulation studies performed during this period were always normal. Polycythaemia may sometimes develop after successful renal transplantation and patients so affected are prone to develop thrombotic episodes (Swales and Evans, 1969). The haemoglobin of our patient never exceeded 13·8 g % and, therefore, polycythaemia would be an unlikely cause in this instance.

Mesenteric venous thrombosis carries a high mortality although the use of anticoagulants in the postoperative period has helped to reduce this (Naitov and Weismann, 1965). Recurrent thrombosis is not unusual (Qureshi and Mansfield, 1964) and may occur up to 32 months after the original event (Naitov and Weismann, 1965). Despite quite adequate anticoagulation a third episode of thrombosis occurred in our patient, with the result that her portal vein became totally occluded. The remorseless progress of the disease in this case would suggest that the aetiological factor, whatever it may have been, was not removed when the diseased bowel was resected.

Abdominal complications are not uncommon in kidney transplant recipients (Penn *et al.*, 1968; Salaman *et al.*, 1969; Penn *et al.*, 1970; Hadjiyannakis *et al.*, 1971; Powis *et al.*, 1972). They usually take the form of a bleeding peptic ulcer, or perforations of the stomach, duodenum or colon. Pancreatitis may also occur (Renning *et al.*, 1972) and to this list we now add mesenteric venous thrombosis. The condition is rare, however, and although more than 8,000 renal transplant operations have now been performed in the world (Renal Transplant Registry, 1972), no similar cases have so far been described to our knowledge.

Summary

Mesenteric venous thrombosis developed in a patient 9 months after successful cadaveric renal transplantation. Following small bowel resection the thrombosis recurred and ultimately this spread to involve the portal and splenic veins with fatal results.

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The Incidence, Investigation and Treatment of Idiopathic Hypercalciuria

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More than 30 years ago Flocks (1940) reported that among his patients with calcium urolithiasis he had found many individuals with "idiopathic high urine calcium" output who did not appear to be suffering from primary hyperparathyroidism or from any other disorder which is known to cause hypercalciuria. Later, Albright *et al.* (1953) coined the term "idiopathic hypercalciuria" for this syndrome which, they claimed, was usually accompanied by a low plasma inorganic phosphate, and the condition was further defined by Henneman *et al.* (1958). Innumerable cases similar to those described by Flocks have since been reported and there is now abundant evidence that hypercalciuria is found much more commonly among patients with renal stones than among healthy individuals (Sutherland, 1954; Cottet and Vittu, 1955; Hodgkinson and Pyrah, 1958; Harrison 1959; Bulusu *et al.*, 1970; Yendt, 1970).

As soon as reference is made to hypercalciuria it becomes necessary to define the limits of normality for urinary calcium. Published figures vary widely, but over the years there has been a tendency to extend the upper limits. Thus, in this country, Hodgkinson and Pyrah (1958) found that 90% of normal men excrete less than 300 mg/24 hours, the corresponding figure for women being 250 mg/24 hours, whereas the more recent studies of Watson and Dale (1966) and of Bulusu *et al.* (1970) indicate that these limits should be raised to 400 mg/24 hours for men and 300 mg/24 hours for women. Furthermore, the recent papers have emphasised that readings in excess of these can be found in many healthy individuals. There are also certain geographical factors which affect urinary calcium levels. It has been pointed out previously by Rose (1967) that the normal range for 24-hour urinary calcium is different on the 2 sides of the North Atlantic. This is very strikingly illustrated by comparing the actual urinary calcium values of 227 to 347 mg/day of the patients of Henneman *et al.* (1958) with idiopathic hypercalciuria with the normal range of Hodgkinson and Pyrah (1958) of up to 300 mg/day or even more. Most of the patients in the American series would not have been considered hypercalciuric in this country, had not an upper limit of normal to 220 mg of calcium per day being quoted by the American authors. We have taken the view that in this country at this time readings in excess of 350 mg/24 hours in men and 300 mg/24 hours in women constitute "hypercalciuria" and that in patients with renal stone the urinary calcium should be kept below these levels.

Although prolonged control of idiopathic hypercalciuria can be achieved by rather strict limitation of dietary calcium (Dent and Watson, 1965), other methods of treatment which may be more acceptable to patients are now available. Firstly, it is now established that the thiazide diuretics induce a sustained fall in urinary calcium in both normal individuals and in patients with hypercalciuria (Lamberg and Kuhlback, 1959; Lichwitz *et al.*, 1961; Higgins *et al.*, 1964; Duarte and Bland, 1965; Yendt, Gagné and Cohanim, 1966). Harrison and Rose (1968) showed that this effect is not due to any change in absorption of dietary calcium but is probably the result of some alteration in the renal handling of this substance. Secondly, cellulose phosphate also lowers urinary calcium, but by quite a different mechanism. The dietary calcium is bound to the cellulose phosphate in the intestinal lumen and thus becomes unavailable for absorption (Dent, Harper and Parfitt, 1964; Parfitt *et al.*, 1964; Nassim and Higgins, 1965; Rapado *et al.*, 1970).

The majority of reports on the use of these drugs in the treatment of idiopathic hypercalciuria are based on relatively short periods of observation and it is still uncertain whether they are safe and effective agents for the prolonged control of hypercalciuria which would appear to be necessary for the prevention of recurrences of stone. We therefore thought it might be of interest to report our experience with a number of patients with idiopathic hypercalciuria who have been treated with thiazides or cellulose phosphates for periods of 18 months to 7 years. In addition, we wish to report the biochemical findings in our cases of idiopathic hypercalciuria and to call attention to the high incidence of this condition among our patients with urolithiasis.

Patients and Methods

During the period November 1965 to August 1972, 108 patients with renal lithiasis were referred to the Metabolic Out-Patient Clinic at St Peter's Hospital for diagnostic studies and medical treatment. All patients referred were submitted to a searching clinical history and examination. Initial routine investigations included measurements of plasma calcium, phosphorus, uric acid, total protein, urea, creatinine, sodium potassium and bicarbonate. Additional investigations carried out in some, but not in all, cases included measurements of 24-hour urinary oxalate, qualitative tests for cystine in urine, short tests of urinary acidification as described by Wrong and Davies (1959) and skeletal X-ray surveys. Urinary calculi were analysed whenever possible. An attempt was made to assign to each patient a primary cause of renal stone formation. Because of our special interest in idiopathic hypercalciuria, results of investigations have also been considered from patients with this diagnosis who were attending another clinic at St Philip's Hospital. Thus, the total number of patients studied with idiopathic hypercalciuria has been raised to 87.

Plasma calcium was measured by semi-automated E.D.T.A. titration (Glatz and Rose, 1968) and urinary calcium by emission flame photometer (MacIntyre, 1957). Uric acid was measured by the uricase method during the first year (1965/6) and thereafter by Technicon Auto-Analyser, and it was shown that the results were the same by these 2 methods. Plasma inorganic phosphate was measured by Technicon Auto-Analyser, plasma proteins by the copper sulphate method in the first year and thereafter by refractometer. Renal calculi were analysed quantitatively using the method of Westbury and Omenogor (1970) and later extended to include estimation of oxalate (Westbury, 1973).

A diagnosis of hypercalciuria was based on the results of analysis of at least 2, or usually 3, 24-hour urine specimens collected when patients were taking their habitual diet, and it was termed "idiopathic" when we could find no evidence of other diseases known to cause hypercalciuria (*e.g.* primary hyperparathyroidism). When this diagnosis was made the patient was advised to avoid milk and cheese in his diet and also calcium-rich medicaments such as "stomach powders". If this was insufficient to lower the urinary calcium to below 350 mg/day in males or 300 mg/day in females, treatment was begun with either a thiazide (almost invariably bendrofluazide 5 to 10 mg/day) or cellulose phosphate (15 to 30 g/day). If the response to the original drug was satisfactory it was continued indefinitely. If the response was insufficient, the other drug was either substituted or added. The majority of patients treated with thiazides also received potassium supplements.

All patients treated with these drugs have been seen at intervals of 3 to 4 months. Follow-up studies have included measurements of urinary calcium, creatinine and sodium, and of plasma calcium, phosphorus, total protein, uric acid, sodium, potassium, bicarbonate, urea, alkaline phosphatase and glucose. Plain X-rays of the renal tract and hands have been carried out at yearly intervals. Some of the patients with idiopathic hypercalciuria have been followed in this way for 7 years, others for much shorter periods. In considering here the long-term effects of therapy on urinary calcium, we have included the findings only when therapy has been given for at least 18 months. In assessing the sustained effects of treatment on urinary calcium we have taken the mean of the last 2 results on any given regime.

Results

Diagnosis

The main conditions thought to have been responsible for the occurrence of renal calculi in the patients attending the St Peter's clinic are listed in Table I. The relationships between sex, medullary sponge kidney and idiopathic hypercalciuria in the 87 patients with the latter diagnosis are shown in Table II.

Table I

Primary Cause of Renal Calculi in 108 Patients Attending the St Peter's Clinic

Idiopathic hypercalciuria	66
Urinary infection	10
Cystinuria	6
Primary hyperparathyroidism	4
Medullary sponge kidney (without hypercalciuria)	3
Primary hyperoxaluria	2
Uric acid stones	2
Urinary diversion	1
Corticosteroid therapy	1
No cause Cause not clear Previously in a hot climate	13
	108

Table II

Sex Incidence and Concurrence of Medullary Sponge Kidney in 87 Patients with Idiopathic Hypercalciuria

Males without sponge kidney	77
Females without sponge kidney	5
Males with medullary sponge kidney	4
Females with medullary sponge kidney	1
	87

Ratio of total numbers of males to females = 13·5:1

Age

The age at the time of presentation for medical investigations of 82 males with idiopathic hypercalciuria varied from 15 to 60 with a mean of 42·3 years. However, the distribution was skewed to the latter age groups as shown in Figure 1 and therefore no S.D. for age has been calculated.

Plasma Biochemistry

The initial biochemical data on these 82 males are shown in Table III, and Figure 2. In correcting the plasma calcium to a total proteins of 6·85%, it is assumed that each 1 g/100 ml of protein

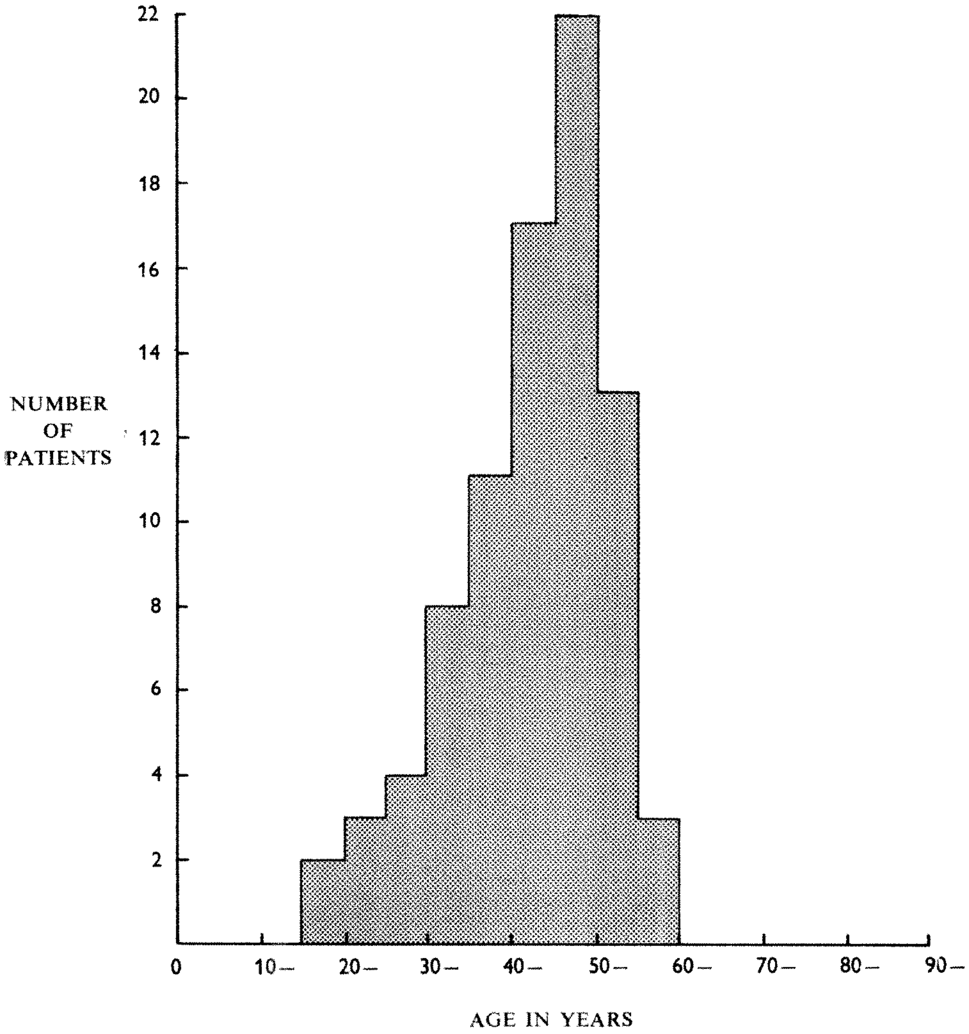

Fig. 1. Age distribution of 83 males with idiopathic hypercalciuria at the time of presentation at St Peter's Hospitals.

combines with 0·75 mg/100 ml of calcium. Because the normal ranges for plasma phosphate and uric acid are dependent upon age and sex, the individual values for these parameters are shown against the means and normal ranges in Figures 3 and 4 respectively.

Stone Analysis

The results of the first quantitative stone analysis from each of 28 males with idiopathic hypercalciuria are available. The mean calcium content was 26·8% s.d. 5·0% and the oxalate content was 39·4% s.d. 13·4%. The main other anion was phosphate and this showed a bimodal distribution. Thus 8 out of 28 contained less than 3% phosphorus and in the remaining 20, the mean phosphorus content was 8·48% s.d. 4·10%. Carbonate was present in 3 stones only and 2 of the patients were known to have had recurrent urinary tract infections as a complication. Uric acid

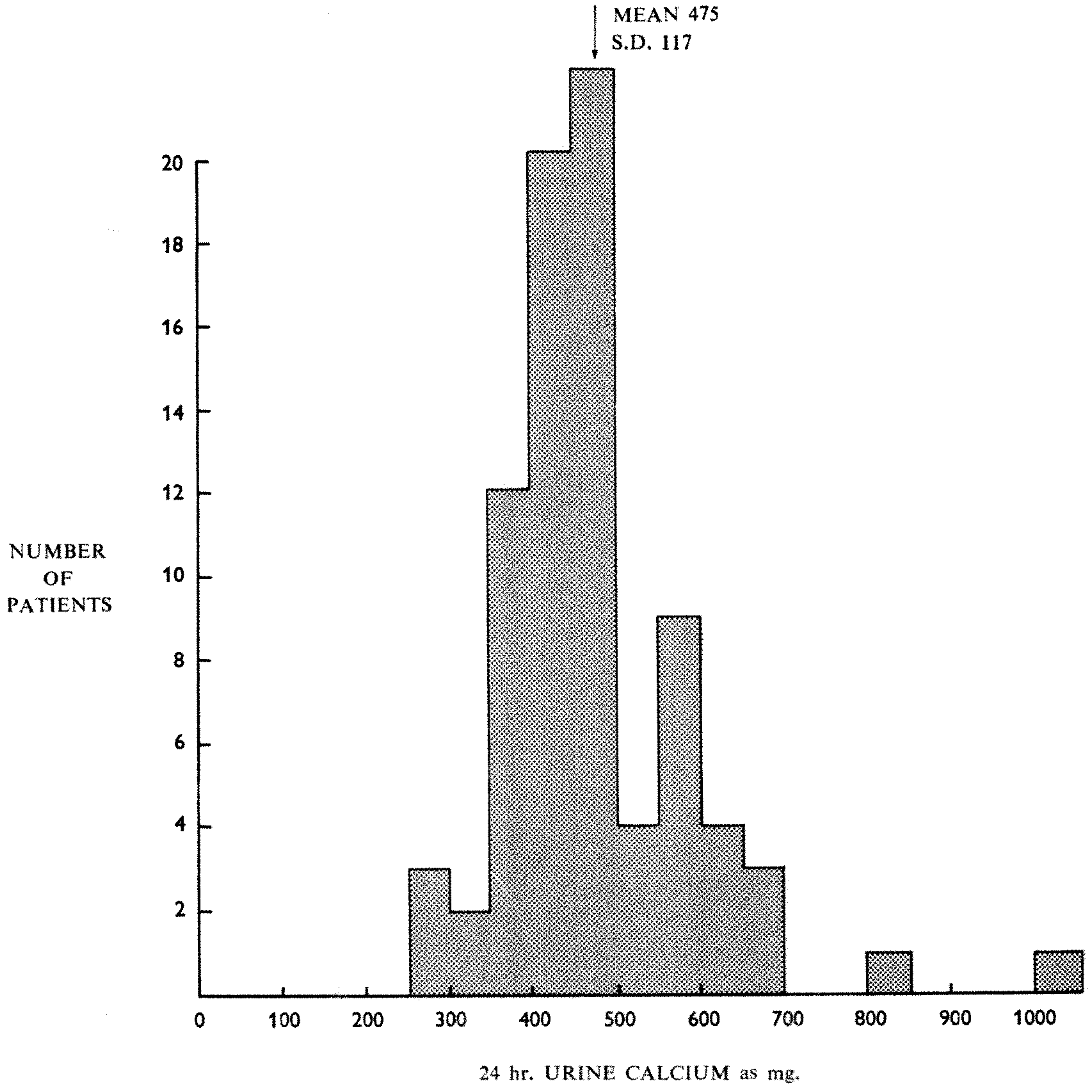

Fig. 2. Distribution of initial urinary calcium values prior to treatment in 80 males with idiopathic hypercalciuria. The 5 patients with urinary calcium values below 350 mg/24 hours later showed higher values.

was detected in 1 stone only and then only in a very small amount (0·6%). Magnesium was undetectable in 9 stones and present in small amounts (0·1% to 0·5%, mean 0·26%) in 19 stones. Results from the first stone analysed from each of 4 female patients with idiopathic hypercalciuria are shown in Table IV.

Treatment with Thiazides

The results of treatment with bendrofluazide alone of 46 patients with idiopathic hypercalciuria are detailed in Table V. An example of satisfactory response is shown in Figure 5 and an example

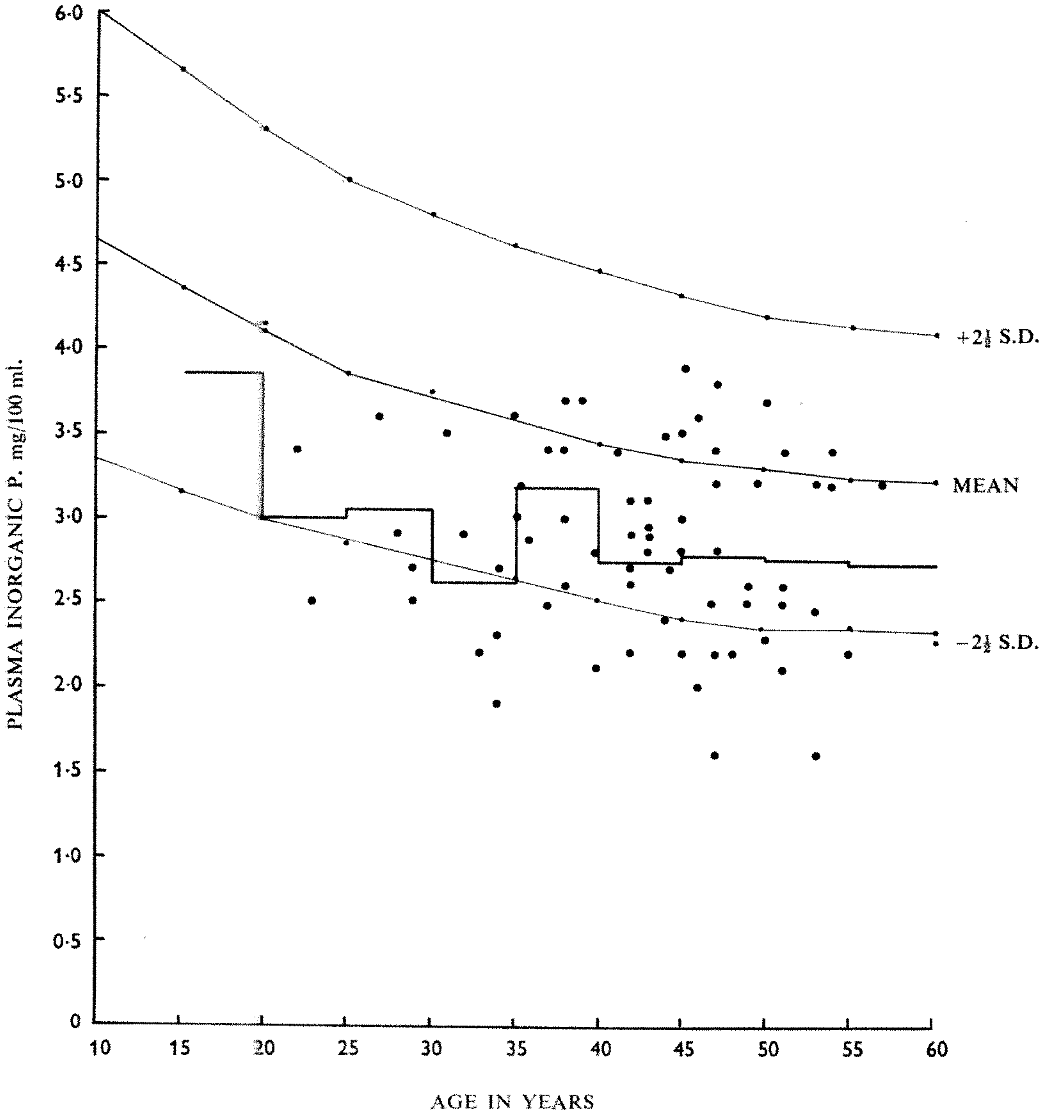

Fig. 3. A comparison of plasma inorganic phosphorus plotted against age for normal male subjects and for 82 males with idiopathic hypercalciuria. Each point represents 1 patient prior to medical therapy and the thick line is the mean for each 5-year group of patients. The thin lines show the mean and ±2½ s.d. as replotted from the data of Greenberg, Winters and Graham (1960).

of "escape" of control in urinary calcium after good control at first as shown in Figure 6. One of the patients who showed a satisfactory and sustained fall in urinary calcium subsequently had to discontinue therapy for a time on account of severe potassium depletion associated with carbenoxolone therapy given for a peptic ulcer. Otherwise, potassium depletion was not a problem. No patient developed gout.

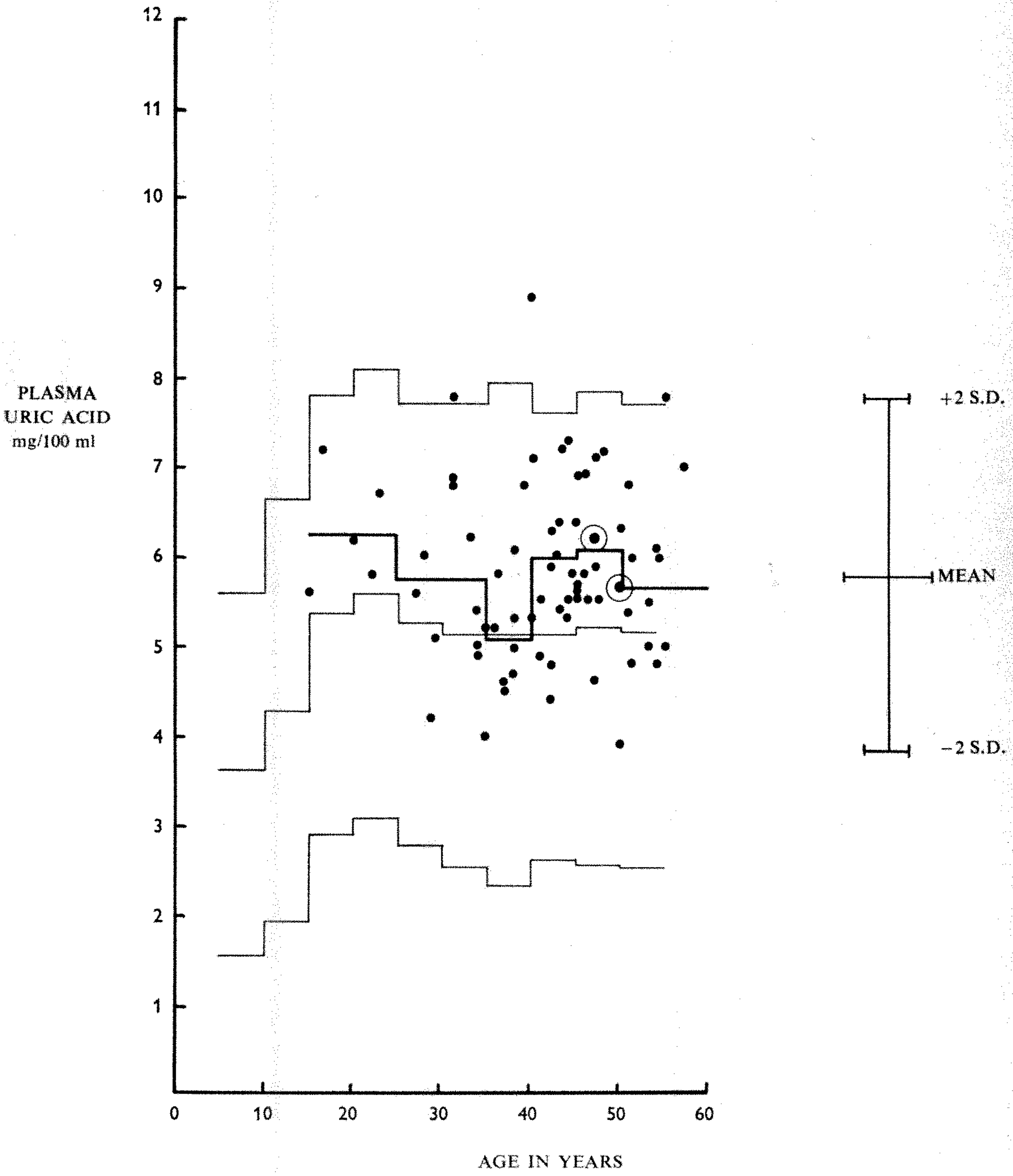

Fig. 4. A comparison of plasma uric acid plotted against age for normal males and 82 males with idiopathic hypercalciuria. Each point represents 1 patient (a circled dot = 2 patients). The thick line is the mean for each 5-year group of patients, and the overall mean with ±2 s.d. for the patients is shown on the right. The thin lines show the mean ±2 s.d. for normal subjects as reported by Mikkelsen and Valkenburg (1965).

Table III

Initial Biochemical Data in 82 Males with Idiopathic Hypercalciuria Prior to Medical Therapy

	Mean	S.D.	
Plasma Calcium (uncorrected)	9·80	±0·47	mg/100 ml
Plasma Calcium (corrected to total proteins of 6·85%)	9·42	±0·45	mg/100 ml
Plasma Inorganic Phosphorus	2·86	±0·55	mg/100 ml
Plasma Uric Acid	5·83	±0·98	mg/100 ml
24-hour Urinary Calcium	475	±117	mg

Table IV

Percentage Composition of Renal Calculi in 4 Female Patients with Idiopathic Hypercalciuria

	Calcium	Phosphorus	Oxalate	Magnesium	Ammonium	CO_2	Uric
S. C.	28	13	Present	0·9	Nil	Nil	Nil
S. F.	35	15	22	0·5	Nil	Nil	Nil
G. F.	11	15	Present	8·0	0·7	+	0·3
C. C.	31	13·5	17	0·3	Nil	Nil	Nil

Table V

Results of Treatment of 46 Patients with Idiopathic Hypercalciuria with Bendrofluazide alone

Sustained satisfactory fall in urinary calcium	25
Partial but insufficient fall in urinary calcium	3
Fall in urinary calcium sufficient at first but subsequent "escape"	5
No appreciable fall in urinary calcium	9
Treatment soon stopped because of onset of diabetes mellitus	2
Treatment soon stopped because of fatigue and lassitude	2
	46

Treatment with Cellulose Phosphate

The results of treatment of 24 patients with cellulose phosphate with or without thiazide are detailed in Table VI. The only troublesome side effect was diarrhoea and/or offensive stools. This occurred in only 6 patients but in these cases was sufficiently severe to prevent treatment with any clinically significant dose.

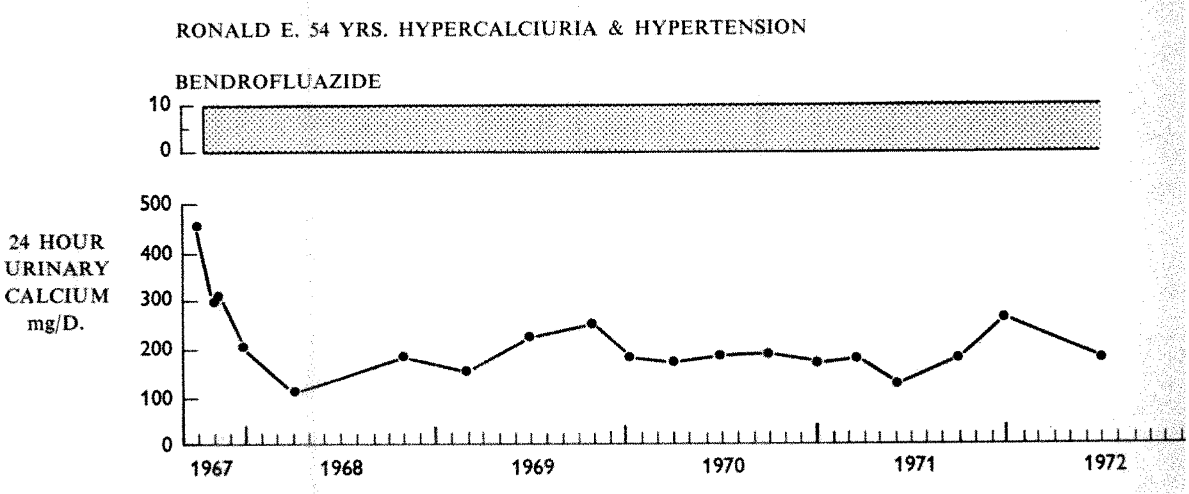

Fig. 5. Example of successful long-term treatment of a patient with idiopathic hypercalciuria with bendrofluazide. The initial hypercalciuria (the mean of several values is shown) was promptly eliminated, and the urinary calcium has remained well below the target figure of 350mg/day for 5 years during which the patient has formed no more stones. Treatment is continuing.

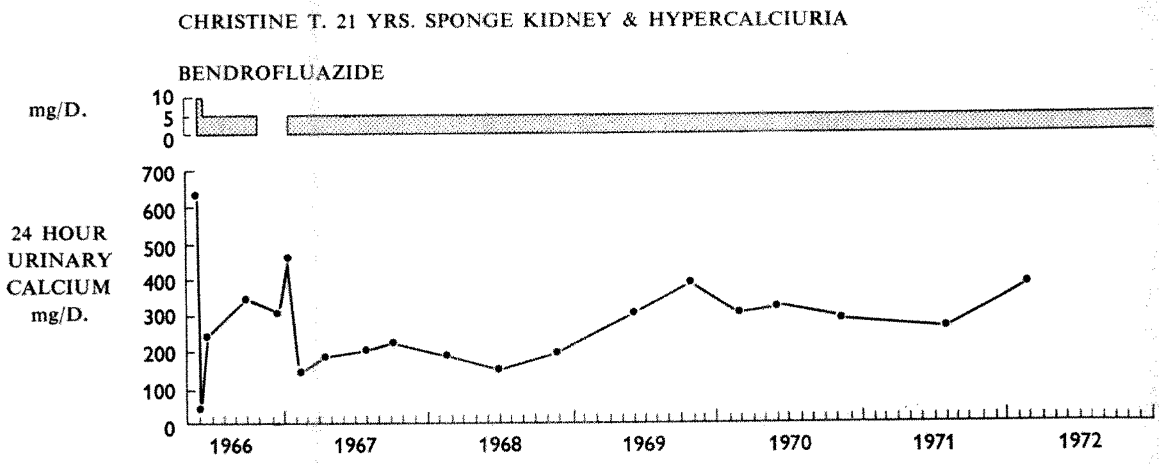

Fig. 6. Example of successful control of hypercalciuria with bendrofluazide, followed by "escape" after about 3½ years of treatment.

Discussion

In considering the causes of renal calculi listed in Table I, it must be appreciated that all the diagnoses are not mutually exclusive. In particular, idiopathic hypercalciuria and urinary infection frequently occurred together and when this has been the case the former has been taken as the primary cause, and the infection considered a result of renal calculus rather than its cause. Table

I shows that idiopathic hypercalciuria was present in 66 of the 108 (61%) patients investigated for renal calculi so that this diagnosis represents by far the most common primary cause encountered. Whether or not this high incidence of idiopathic hypercalciuria would be reflected in the mass of stone formers in the whole population is a matter for conjecture. On the one hand it must be admitted that these patients did not form a consecutive series of unselected stone formers admitted to a hospital, but are a special group referred mainly from surgical colleagues for investigation. It is clear that certain selection has occurred. Thus it will be noted that there are no children under 15 years of age, and the incidence of primary hyperparathyroidism is lower than might be expected since patients with this diagnosis were admitted direct to the wards rather than to this particular clinic, and there could be other factors also tending to increase the incidence of idiopathic hypercalciuria. On the other hand, the present series has striking similarities to the study of Yendt (1970) who found 42% of 439 stone formers had idiopathic hypercalciuria. The 2 series are also alike in the ratio of males to females with idiopathic hypercalciuria, both series showing a very marked preponderance of males. The incidence of idiopathic hypercalciuria is so high in both series that, even allowing for possible distortion due to selection of cases, this condition must be the most common cause of renal stone formation in adult males in both this country and Canada.

It was found by Ekstrom *et al.* (1959) that about one-third of patients with medullary sponge kidney also had hypercalciuria. In the present series only 3 cases were found to have medullary sponge kidney without hypercalciuria (Table I) while 5 cases were found to have both diagnoses (Table II). Hence the incidence of hypercalciuria in this small series of patients with medullary sponge kidney who also had renal calculi was 5 out of 8, or 63%.

The initial biochemical data are of some interest. The plasma calcium values are indistinguishable from the published normal range for the same method, confirming the observations of Henneman *et al.* (1958). It is stressed that there is no evidence of a "tendency to a low plasma calcium" which others have thought to be present (Albright and Reifenstein, 1948). We do confirm that the plasma inorganic phosphorus is low in idiopathic hypercalciuria (Table III) although, when age and sex are taken into consideration, as in Figure 2, the mean plasma phosphorus is only about 0·5 mg/100 ml below the normal mean. It must also be stressed that most of the blood samples were from out-patients at about mid-morning and this also leads to lower results than in fasting early morning samples, so that the true difference between plasma phosphorus levels of the patients and the normals must be even less than 0·5 mg/100 ml.

Table III shows that the mean plasma uric acid levels in our hypercalciuric patients was 5·83 mg/100 ml. However, allowance must be made for age and sex, and when this is done, as in Figure 3, it can be seen that the mean level is only about 0·5 mg/100 ml above the normal mean. Furthermore, most of the results are from non-fasting out-patients, so that the true difference may well be less than 0·5 mg/100 ml. These results contrast with the remarkable findings of Smith *et al.* (1969). These authors admittedly did not refer to idiopathic hypercalciuria as such, but did report elevations in plasma uric acid of some 3 mg/100 ml in patients with cystine, calcium oxalate and mixed calcium oxalate—phosphate renal stones. It is hard to understand the difference between these 2 sets of results, although 1 point can certainly be made. Whereas none of our patients had elevated serum urea or creatinine levels, Smith *et al.* (1969) said that "No patient was excluded if renal failure was present". However, this is hardly likely to explain so great a difference in the uric acid levels since the mean serum creatinine levels in each group given by Smith *et al.* (1969) are only minimally raised.

Quantitative stone analysis reveals that out of 28 stones analysed (1 per male patient only), all were rich in calcium, 5 contained calcium and oxalate only and a further 12 contained calcium phosphate and oxalate only. Magnesium was present in small quantities in 19. Thus the majority of the stones contained either calcium oxalate alone or calcium phosphate and oxalate, possibly with traces of magnesium. In no case was oxalate absent, the lowest oxalate content observed having been 15%. This supports the view that calcium oxalate is the first material to crystallise out into stone formation and that the other salts are deposited subsequently. In the case of the females, the situation was quite different, as can be seen in Table II. There are too few stones to permit statistical analysis but it is clear that the phosphorus and magnesium contents were higher. This was attributed to recurrent urinary infections having complicated the situation.

As stated above, our criterion of success in treating idiopathic hypercalciuria has been the reduction of urinary calcium to 350 mg/day or less for males and to 300 mg/day or less for females. By this criterion the long-term success rate with bendrofluazide alone was 54% (25/46). The incidence of side-effects was not unduly high and neither were they too distressing. Diabetes mellitus was unmasked in 2 cases, but the condition was rapidly diagnosed and cleared up quickly on stopping the treatment. In 2 other cases the treatment had to be stopped quite soon on account of fatigue and lassitude. Severe potassium depletion occurred in 1 patient, who had previously been successfully treated with bendrofluazide, when he was also given carbenoxolone because of a duodenal ulcer. This latter drug is known to cause potassium depletion and we have subsequently avoided using it in conjunction with thiazides. We have noticed that 5 of the patients showed an initial satisfactory fall in urinary calcium but with a gradual escape from the effect and an example of this is shown in Figure 6. In 9 patients (20%) there was complete failure to obtain a fall in urinary calcium. Some of these patients showed other metabolic effects of thiazide, *viz.* fall in plasma potassium and rise in plasma uric acid but others showed very little or no change in these parameters. One patient, for example, showed almost no change in any parameter despite 15 mg/day of bendrofluazide and he was thought perhaps not to be taking the tablets, but on changing to cellulose phosphate, which is much more inconvenient to take, there was a rapid fall in urinary calcium and it therefore seems more likely that bendrofluazide was metabolically inactive in this patient.

Another cause of difficulty was encountered in 2 patients who responded well to thiazide when in the ward but went out of control as out-patients. It was noted that the urinary sodium values were high as out-patients and on questioning they both admitted to putting a lot of salt on their food at home. A correlation between urinary sodium and calcium has been reported by King, Jackson and Ashe (1964) and by Modlin (1966) and we therefore subsequently advised patients to retrict the salt added at the table.

Plasma uric acid values generally rose with thiazide therapy by about 1 to 5 mg/100 ml and values as high as 11 mg/100 ml have occurred. Gout, however, has not resulted, and values as high as this are not the rule. Low plasma potassium values have generally developed eventually unless potassium supplements were given. The hypokalaemia was readily reversed by giving potassium supplements, generally "slow-K".

It was rather a surprise to find that 25% (6/24) of the patients treated with cellulose phosphate objected to carrying on with it because of diarrhoea or offensive stools. The remainder of the patients treated with this drug did well and showed a satisfactory fall in urinary calcium in nearly every case (see Table VI), and no other side-effects were noted. The results of a combination of cellulose phosphate and thiazides were good in every case where prolonged treatment was not prevented by side-effects.

As shown in Table VII, there was an overall success rate in reducing urinary calcium values to acceptable levels in 75% of the patients with idiopathic hypercalciuria. This figure is highly encouraging. Although there remain 25% who have not been fully under control, not all the "failures" have yet been tried on both thiazide and cellulose phosphate together. Thus, Tables VI and VII also reveal that while the "success" rates for bendrofluazide and cellulose phosphate given separately are rather similar, there is a striking improvement when the 2 drugs are given together. There has been no "failure" with this combined treatment when given in the long term. This synergistic effect of the 2 drugs is what would be expected given that thiazides act upon the kidneys and cellulose phosphate acts on the alimentary tract (see above). Nevertheless it remains our policy to recommend thiazides as the drug of first choice, unless there is a specific contra-indication (diabetes, gout), since they are cheap and small tablets that can easily be taken at any time of day. By contrast, cellulose phosphate is very expensive, very bulky to carry around, and has to be taken with the main meals. Nevertheless, we are convinced that cellulose phosphate has a real part to play in the treatment of idiopathic hypercalciuria when thiazides are ineffective or are contraindicated, or else in conjunction with thiazides.

Table VI

Results of Treatment of 24 Patients with Idiopathic Hypercalciuria with Cellulose Phosphate

Cellulose phosphate therapy alone	15
Cellulose phosphate combined with thiazide	9
Cellulose phosphate discontinued or severely reduced because of diarrhoea and/or offensive stools	6
Satisfactory long-term control with cellulose phosphate alone	9/11
Partial but insufficient control with cellulose phosphate alone	2/11
Satisfactory long-term control with cellulose phosphate plus thiazide	7/7

Table VII

Overall "Success" Rate in Lowering Urinary Calcium

		%
Total number of patients treated	55	
"Success" in 46 patients treated with thiazide alone	25	54
"Success" in 15 patients treated with cellulose phosphate alone	9	60
"Success" in 7 patients treated with both drugs together	7	100
Total successes	41	75

We have not yet attempted to correlate the effect of lowering urinary calcium with the rate of stone recurrence. Yendt *et al.* (1970) showed a fall in recurrence rate on treating stone formers with thiazide, but it seems that there is a difference in the rate at which stones recur in individual patients on the two sides of the North Atlantic, with less frequent recurrence on this side. Hence we will have to continue for longer before definite conclusions can be reached. Meanwhile we have a very strong clinical impression that renal stone formation has not progressed in those patients in whom the control of urinary calcium has been achieved and maintained.

Despite the warning of Harrison and Rose (1968) that long-term use of thiazides might possibly lead to ectopic calcification, there has been no evidence of this in the current long-term study. X-rays of soft tissues have shown no evidence of ectopic calcium and renal function has not apparently deteriorated. This again raises the question of the destination of the calcium which is prevented from excretion through the kidneys by thiazides. There are only 3 possibilities namely, increased faecal excretion, increased bone formation (or reduced bone loss), or deposition in soft tissues. Harrison and Rose (1968) eliminated the first possibility in studies of up to 24 days of treatment, but the possibility of long-term adaptation remains as a possibility. The third possibility seems to be eliminated by the lack of ectopic calcification reported here. It is therefore possible that a by-product of thiazide therapy is a reduction of the normal negative calcium balance and development of osteoporosis seen in mature adults (Rose, 1967).

Conclusion

Idiopathic hypercalciuria is the most common single cause of renal calculi found in this country. In adult males there is an absolute majority of the patients with this condition. It was found in well over 50% of adult male stone formers.

The raised urinary calcium can be reduced to more acceptable levels in the great majority of cases by treatment with bendrofluazide and/or cellulose phosphate. Such treatment has remained effective for periods as long as 7 years.

It is recommended that idiopathic hypercalciuria should be sought vigorously amongst stone formers and treated when found.

Summary

A hundred and eight patients with renal calculi attending a single clinic were studied in order to try and establish the primary cause of their stones. Sixty-six of these patients (61%) proved to have idiopathic hypercalciuria, confirming that this is the most common cause of renal calculi in adult males.

A total of 87 patients with idiopathic hypercalciuria were investigated. Plasma calcium was normal with no "tendency to a low plasma calcium", plasma inorganic phosphate was only 0·5 mg/100 ml below normal, and plasma urate only 0·5 mg/100 ml above normal.

The long-term effect on the urinary calcium of patients with idiopathic hypercalciuria treated with bendrofluazide and/or cellulose phosphate has been studied. The success rate in lowering urinary calcium was 54% for thiazide alone, 60% for cellulose phosphate alone, and 100% in the small number treated with both drugs together. The overall success rate was 75%, but may yet rise further.

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Some Aspects of the Adult Urinary Stone Problem in Great Britain and Northern Ireland

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The examination of the composition of individual urinary stones may be part of an immediate medical service, or of a continuing medical research, or it may contribute to both of these projects. Thus in the diagnosis and treatment of the various types of urolithiasis, detailed information on the composition of the calculus or calculi formed plays an important role. If the results of such analyses are then collected, or all the stones from say a particular geographic area or a particular type of patient are studied, data on the distribution of the various types of urolithiasis with respect to the variables chosen can be obtained. Information of this nature could well be important in understanding the aetiology and epidemiology of urinary calculi.

Although the composition of stones in many countries has been studied by techniques ranging from simple chemical analysis to sophisticated methods of identifying individual compounds, very few papers give details of a quantitative analysis or correlate stone composition with variables such as age and sex of patient, the site, weight and number of stones, etc. In 1966 we started an investigation aimed at relating the composition of urinary calculi from different parts of the world and from different periods in history with any available relevant information. The overall composition of some stone collections giving a picture for their particular area has already been published (Lonsdale, Sutor and Wooley, 1968*a* and *b*; Sutor and Wooley, 1969*a*, 1970, 1971, 1972). In a further set of papers we plan to present the results of a computer study of data collected on 2,533 stones. This paper, which is the first in the series, gives details of the type and relative prevalence of adult urinary stones in Great Britain and Northern Ireland today and of the people most likely to form them. It is based on 856 stones from 16 centres and includes the preliminary results already published on the overall composition of stone collections from Norwich (Lonsdale *et al.*, 1968*a*), Leeds (Sutor and Wooley, 1970), Glasgow (Sutor and Wooley, 1971) and Northern Ireland (Sutor and Wooley, 1972). The survey was not, however, designed to give the total incidence of stone disease in relation to population figures in Great Britain and Northern Ireland.

Material and Methods

The 856 stones included in this survey were kindly provided by surgeons and physicians from the following centres and cities: Belfast (66 stones), Bradford (39), Bristol (52), Dundee (78), Glasgow (207), Hammersmith Hospital, London (33), Leeds (121), Newcastle (30), Norwich (68), Oxford (14), Reading (41), Royal Naval Hospital, Gosport (79) and 4 London hospitals (28), making a total of 505 for England, 285 for Scotland and 66 for Northern Ireland. No specimens were received from Wales.

In order that the collection be representative, as far as possible, of each region and hence of Great Britain and Northern Ireland, the stones were not selected in any way but were collected over a period of several months or years as the patients presented for operation in the areas concerned until about 50 to 100 of both upper and lower urinary tract stones were obtained. In many areas this target was not always reached but such smaller collections are included since they are representative of that area. For each stone we requested details of its site, whether it had been removed surgically or had been passed, the patient's age, sex, occupation and previous history of the disease (if any). Unfortunately, the patient's clinical details and biochemical data were not always available and could not be included in this survey.

The identity of the crystalline compounds present in the stones and the sequence in which they were laid down were determined by the X-ray powder method using techniques described previously (Lonsdale *et al.*, 1968*a*; Sutor and Wooley, 1969*b*). From the intensity of the diffraction patterns, an approximate quantitative estimation was made of the relative amount of material present in mixed samples. Each component identified in a stone was weighted according to the amount found in the different stone areas, *i.e.* the nucleus, interior and surface, using the scheme described in a previous paper (Lonsdale *et al.*, 1968*a*). These values could then be averaged over a particular group of stones to obtain the weighted percentage composition of each constituent present. The method has certain advantages over presenting the results in terms just of major stone components which has often been used previously, since it shows that collections contain observable quantities of a compound although it may never occur in that collection as a major component. Although the method does not give the quantitative composition of the stones exactly, it is a good approximation to the relative amounts of the various constituents present.

The following information was coded and punched on computer cards: the patient's identification number, country and town of residence, age, sex and previous stone history, the number of stones formed, their total weight and their site in the urinary tract, when and whether they were removed or passed and the weighted composition of the nucleus, interior and surface of each. For convenience in coding, stone weights were rounded off to one significant figure. If a patient had multiple calculi or was a recurrent stone-former, the individual analyses were averaged and combined under a single entry with appropriate information under the headings of number of stones formed or previous history. Patients were also classified according to their occupation into the 5 Social Class Groups listed in the General Register Office's Classification of Occupations (1960) issued prior to the 1961 Census of population.

A program especially written for the IBM 360/65 computer at University College London could be used to calculate the number of stones containing some stated quantity of one or more compounds, the weighted percentage composition of constituents in the whole stones or in different areas, the frequency of occurrence of constituents and the compound or compounds often associated with them, etc. for groups of stones selected by setting allowable ranges for the relevant variables. The program could also be linked with Stanford University's program "Statistical Package for the Social Sciences" to obtain means, standard deviations and errors and to carry out statistical analyses.

Results

Constituents and Types of Urinary Stones

Out of the 856 stones, only 325 consist of a single crystalline substance or of a mixture of different hydrates or forms of a compound such as the hydrates of calcium oxalate or the different forms of calcium phosphate. Most of the stones (531) are of mixed composition.

The crystalline constituents found in this X-ray study, their abbreviated nomenclature used throughout our papers, the frequency of their occurrence and the weighted percentage amount of each in the whole collection are shown in Table I and discussed below.

Calcium Oxalates

The most abundant and frequently occurring constituents in the collection are the mono- and di-hydrates of calcium oxalate (Table I), but significantly more stones contain the monohydrate compared with the dihydrate ($P < 0{\cdot}01$) and there is more of it. Alone or combined these 2 compounds account for 233 (72%) of the 325 pure stones, the most common type of all being that composed of a mixture of both (Table II).

Of the 531 stones of mixed composition in the whole collection, 357 (67%) contain either or both of the calcium oxalates generally in association with some form of calcium phosphate, and

Table I

The Crystalline Constituents, their Frequency of Occurrence and the Weighted Percentage Amount of Each in the Collection of Stones from Great Britain and Northern Ireland

Constituent	Abbreviated Nomenclature	Percentage No. of Stones with Constituent	Weighted Percentage Amount in Collection
Uric acid	A1	2·3	1·1
Uric acid dihydrate	A2	1·3	0·5
Ammonium acid urate	B	2·6	0·5
Sodium acid urate monohydrate	J	0·4	0·1
Calcium oxalate monohydrate (whewellite)	C1	63·4	28·0
Calcium oxalate dihydrate (weddellite)	C2	50·4	22·3
One or both of the calcium oxalates	...	68·9	50·3
Cystine	D	1·5	1·4
Carbonate-apatite	F1	35·8	18·6
Hydroxyapatite	F2	37·6	12·7
Calcium hydrogen phosphate dihydrate (brushite)	F3	2·1	0·9
β-Calcium phosphate (whitlockite)	F4	4·8	1·4
Octacalcium phosphate	F5	2·2	0·5
One or more of the calcium phosphates	...	67·1	34·1
*Magnesium hydrogen phosphate trihydrate (newberyite)	G1	0·9	0·1
Magnesium ammonium phosphate hexahydrate (struvite)	G2	25·4	10·9
Traces of unidentified material	X	1·1	0·1
Foreign bodies, rare unidentified constituents	H	1·8	0·9

* Not a primary constituent, formed by decomposition of struvite.

Table II

Number of Pure Stones

Constituent(s)	Number of Stones
Mixed calcium oxalates	167
Calcium oxalate monohydrate	53
Mixed calcium phosphates	23
Carbonate-apatite	21
Calcium oxalate dihydrate	13
Cystine	11
Hydroxyapatite	8
Mixed carbonate- and hydroxy-apatite	7
Struvite	7
Mixed uric acids	5
Unidentified compounds	5
Anhydrous uric acid	3
Ammonium acid urate	1
Brushite	1

have the following composition: calcium oxalate + calcium phosphate—293 stones; calcium oxalate + calcium phosphate + one or more other constituents—50; calcium oxalate + other constituents (but no calcium phosphate)—14. Calcium oxalate and calcium phosphate therefore occur together in 96% of these stones and in 65% of the 531 stones of mixed composition. Apatite is the calcium phosphate most frequently associated with the oxalates being present in all but 5 of the 343 stones containing both calcium oxalate and calcium phosphate. Table III gives the different combinations of calcium oxalate monohydrate and/or dihydrate with hydroxyapatite and/or carbonate-apatite and shows that it is hydroxyapatite which is usually associated with either or both of the oxalates. Such a combination occurs in 89% of the stones composed of calcium oxalate + calcium phosphate, and in 83% of those composed of calcium oxalate + calcium phosphate + other constituents but not struvite. This compound was excluded since the next section demonstrates its relationship with carbonate-apatite.

Table III

Combinations of Constituents in the 531 Stones of Mixed Composition. See Table I for key to symbols. "Others" can be one or more of the constituents except C1, C2, F1, F2 and G2

Reference Constituent(s)	No. of Mixed Stones containing Reference Compound(s)	Frequency of Occurrence of Certain Constituents with Reference Compound						
		F1	F1 + others	F2	F2 + others	F1 + F2	F1 + F2 + others	Remainder
C1	83	10	3	42	10	6	3	9 (1 with G2)
C2	26	2	...	15	3	...	1	5
C1 + C2	209	14	2	166	6	15	1	5 (2 with G2)
C1 and/or C2 + G2	39	26	3	...	...	9	1	...
G2	171	125	27	3	2	6	3	5 (3 with C1 and/or C2 also listed above)
Remainder	6	...	3	...	1	...	1	1
Totals*	531	215		248		46		22

* Less 3 duplicated stones in "Number" and "Remainder" columns.

Calcium Phosphates

Carbonate-apatite and hydroxyapatite are the most important constituents after the calcium oxalates, but, although each occurs in the same number of stones, the total amount of the former exceeds considerably that of the latter (Table I). The remaining calcium phosphates—brushite, whitlockite and octacalcium phosphate—are not frequent constituents of urinary calculi (Table I). Taken collectively, the calcium phosphates occur in almost as many stones as the calcium oxalates but the total amount of oxalate is very much greater (Table I) since there are 4 times as many pure oxalate stones as pure calcium phosphate. Only 60 stones consist of 1 or more of the calcium phosphates (Table II), the most common varieties being the mixed type (23 stones) and carbonate-apatite (21).

Either or both the apatites, sometimes with other calcium phosphates, are present in 509 of the 531 stones of mixed composition in the collection (Table III), and another 5 contain brushite and occasionally octacalcium phosphate. Calcium phosphate mainly as apatite is therefore the most important general constituent of stones of mixed composition being present in 97% of them.

The compounds most frequently associated with apatite in these calculi are the calcium oxalates and/or struvite, any other combination is relatively unimportant (Table III). As already demonstrated, hydroxyapatite is the form which almost invariably crystallises with the calcium oxalates, and Table III shows unequivocally that carbonate-apatite is usually laid down with struvite. Of the 215 stones containing carbonate-apatite but no hydroxyapatite, struvite is present in 84%. Many of these calculi consist entirely of carbonate-apatite + struvite, and in most others, the sequential deposition is such that these 2 constituents can again be linked.

No definite pattern of occurrence can be established for the other calcium phosphates though some general observations are possible. Brushite, whitlockite and octacalcium phosphate are frequently present in stones of complex composition in that as many as 6 different constituents are present. These are the calcium oxalates and other calcium phosphates but not uric acid or the urates. Brushite was not found in any stone with struvite, but the occurrence of whitlockite and octacalcium phosphate with struvite in definite stone layers suggests they too may form in infected urine under suitable conditions.

Magnesium Phosphates

Struvite is the only primary constituent in this group since newberyite in human stones is thought to be a decomposition product (Sutor, 1968). It is the sole constituent of only 7 stones (Table II) but is present in 210 calculi of mixed composition. Of these, 125 consist entirely of carbonate-apatite+struvite, and 75 contain these compounds in close association (Table III). For the 2 component stones, the total weighted percentage amounts of carbonate-apatite and of struvite are the same and these constituents are usually intimately mixed from the nucleus to the surface of the calculus.

Uric Acids

Only 20 stones contain anhydrous uric acid, and of these, 3 consist entirely of this substance and 5 of a mixture of anhydrous uric acid and uric acid dihydrate. Calcium oxalate is present in 11 of the 12 remaining stones, uric acid dihydrate in 6 and urate in 1, but the combinations of these constituents are unimportant. One stone though has a surface deposit of struvite suggesting that infection developed subsequent to stone formation, since uric acid and struvite are laid down in acid and alkaline urine respectively. Uric acid dihydrate occurs in 11 stones and was always associated with the anhydrous form, but other constituents, usually the calcium oxalates, are sometimes present too.

Urates

An interesting finding is a very rare pure stone of ammonium acid urate (Sutor, 1972). The most important type of children's bladder stones from technically-developing countries consists of ammonium acid urate and calcium oxalate, and this variety also occurred in England in the 18th and 19th centuries but died out in the early part of this century (Sutor, 1972). In the present series, 5 stones do, in fact, consist of or contain this combination of constituents, but all are from the Norwich collection which dates from 1932 to 1961 and is the only one comprised of stones removed prior to 1967. As several are also from the bladder, they may represent calculi begun in childhood or be the last examples of an important type from a previous era. All other stones containing ammonium acid urate also contain struvite and carbonate-apatite. These usually form in patients who are often elderly and who have an abnormally high excretion of uric acid and urine infected by urea-splitting organisms (Sutor, 1972).

Sodium acid urate monohydrate is present in 3 stones which also contain some of the oxalates, phosphates or ammonium acid urate.

Cystine

Cystine is not usually associated with other constituents and 11 of the 13 calculi containing it are pure (Table II). However, it is intimately mixed with hydroxyapatite in one, and hydroxyapatite and struvite in the other stone of mixed composition.

Assignment of Stones to Groups according to Composition

Tables II and III indicate that, on the basis of composition, most calculi from Great Britain and Northern Ireland may be assigned to one of a few well-defined groups which have the following names and constituents: C+F stones consisting of calcium oxalate+calcium phosphate usually hydroxyapatite (34% of all stones); C stones made up of pure calcium oxalate (27%); F+G stones composed of calcium phosphate usually carbonate-apatite+struvite (17%); F stones—

pure calcium phosphate (7%); C+F+G stones—calcium oxalate+calcium phosphate+struvite (5%); B+F+G stones—ammonium acid urate+calcium phosphate+struvite (1½%).

To discover whether these groups, selected mainly on empirical grounds, bear any relationship to those obtained by considering the stone constituents from a purely statistical viewpoint, the sample was subjected to a cluster analysis. The constituents were changed to binary form, the value 1 being assigned if a particular compound were present and 0 if it were absent. The 856 calculi were then subdivided successively into 4 clusters (since 2 empirical groups are very small) using the method of monothetic division with the error sum of squares used as the measure of dissimilarity between clusters (Wishart, 1969). Table IV shows the total number of stones and the frequency of occurrence of the constituents in each cluster, while Table V gives the percentage of the membership of each cluster belonging to each empirical group. On the whole, each empirical group falls into a different cluster and mostly dominates that cluster. Rather interestingly, nearly all the stones probably formed in or associated at some time of their growth with urine infected by urea-splitting organisms (*i.e.* F+G, C+F+G and B+F+G stones) are assigned to one cluster. However, in many instances, particularly in the case of some C+F+G stones, the sequential deposition of constituents suggests that infection probably occurred after the stone had nucleated and grown to a certain size so that its aetiology is different from one which formed directly as a result of urinary infection. This would rule out the grouping of all calculi in these composition types, and because the number of cases in the C+F+G and B+F+G groups is small, these groups have usually been omitted from subsequent calculations. Cluster 2 is made up of the C+F stones in which the calcium phosphate is exclusively hydroxyapatite, but those containing some carbonate-apatite either alone or combined with hydroxyapatite and other

Table IV

Distribution of Stone Constituents and Number of Stones in the 4 Clusters

Stone Constituent	Number of Stones containing a Particular Constituent in Each Cluster			
	Cluster 1	Cluster 2	Cluster 3	Cluster 4
A1	...	2	18	...
A2	...	...	11	...
B	13	2	6	1
J	1	...	1	1
C1	31	224	234	54
C2	16	190	190	35
D	...	2	11	...
F1	200	...	...	106
F2	19	262	...	41
F3	1	6	6	5
F4	3	15	...	18
F5	6	4	1	8
G1	4	...	2	2
G2	200	5	12	...
X	4	2	1	2
H	4	1	6	4
Total	200	262	288	106

See Table I for key to symbols for constituents.

calcium phosphates occur in cluster 4 which contains most of the pure calcium phosphate specimens. There seems to be no justification for such a separation, so all C+F stones were grouped together. Cluster 3 contains all the pure calcium oxalate calculi. If the data are split into more than 4 clusters, calcium oxalate monohydrate calculi separate from the other pure oxalate ones and C+F stones divide according to the type of oxalate present. Subdivision into too many groups would be impractical because of the small numbers in each, and so 4 main ones (C, F, C+F and F+G) selected as above have been chosen for subsequent statistical analyses.

Table V

Percentage of the Membership of Each Cluster belonging to Each Group

Group	Cluster 1	Cluster 2	Cluster 3	Cluster 4
F	...	5·4	0·3	42·5
C	...	...	81·3	...
F+G	70·0	1·5	...	...
C+F	...	90·0	1·6	49·1
C+F+G	19·5	...	...	1·9
B+F+G	6·0	...	...	...
Other	4·5	3·1	16·8	6·6

Key: B = ammonium acid urate, C = calcium oxalate, F = calcium phosphate, G = struvite.

Data for All Stones and Patients

There are 659 cases of upper urinary tract stones (416 kidney, 243 ureteric) and 165 lower urinary tract ones (161 bladder, 4 urethral). The patients are comprised of 555 males and 279 females with an age range of 21 to 89 years. The number of stones formed at a time ranges from 1 to 190, but single stones predominate, being present in 577 cases compared with 155 examples of multiple calculi. The total weight of stones from a patient irrespective of the number formed varies from 0·001 to 200 g.

Breakdown of Data according to the Main Variables

In order to determine any relationships among sex or age of patient, composition, site, weight or number of stones, the data were subdivided using these variables. Because of the limited number of cases, only 2 age-groups were taken into account: first, patients aged 21 to 49 years, and second, those over the age of 49. Similarly, the number of stones formed was divided into 2 categories—only 1 stone, and 2 or more. Three sites in the urinary tract were considered—kidney, ureter and bladder, the few urethral stones being included in the last one.

Incidence of Stones in relation to their Site in the Urinary Tract and the Age and Sex of the Patient

The 1966 Census tables were used to calculate the number of females and males in the 2 age-groups for the entire population of Great Britain and Northern Ireland. Comparison of the number of cases of kidney, ureteric and bladder stones with these figures (Table VI) shows that men are more likely than women to form all these types of calculi in both age-groups and that the differences for both ureteric and bladder stones are highly significant ($P < 0{\cdot}001$) except for the very small number of bladder stone patients in the younger group. However, although men are more likely to form kidney stones than women, the difference between the sexes is not so great as for the other stone sites ($P < 0{\cdot}05$ for the younger group and $P < 0{\cdot}01$ for the older). The distribution of kidney, ureteric and bladder stones with age is similar for the sexes. There is no difference in the number of ureteric stones, however, there are significantly more kidney stones in the younger group ($P<0\cdot001$ for females and $P<0\cdot05$ for males) and significantly more bladder calculi in the older group ($P<0\cdot01$ for females and $P<0\cdot001$ for males).

Table VI

Number of Males and Females in the 2 Age-groups with Kidney, Ureteric and Bladder Calculi compared with the Total Number of Persons of the Same Age and Sex in the Population

Sex or Age	Total Number in Population	Number of Stone Cases in		
		Kidney	Ureter	Bladder
(a) *Females and males aged 21 to 49*				
F	9,837,468	116	41	5
M	9,752,599	149	97	12
		$P<0\cdot05$	$P<0\cdot001$	$P>0\cdot05$
(b) *Females and males aged 50 and over*				
F	9,318,413	58	29	19
M	7,308,065	79	73	117
		$P<0\cdot01$	$P<0\cdot001$	$P<0\cdot001$
(c) *Females by age*				
21-49	9,837,468	116	41	5
50 and over	9,318,413	58	29	19
		$P<0\cdot001$	$P>0\cdot05$	$P<0\cdot01$
(d) *Males by age*				
21-49	9,752,599	149	97	12
50 and over	7,308,065	79	73	117
		$P<0\cdot05$	$P>0\cdot05$	$P<0\cdot001$

Table VII

Number of Stones classified according to the Age and Sex of the Patient, and the Site in the Urinary Tract and Composition Group of the Stone

Sex	Female						Male					
Age (years)	21-49			50 and over			21-49			50 and over		
Site of Stone	Kidney	Ureter	Bladder	Kidney	Ureter	Bladder	Kidney	Ureter	Bladder	Kidney	Ureter	Bladder
Composition group												
F	2	8	1	5	3	1	7	2	1	5	3	12
C	11	6	1	15	10	...	57	48	1	17	37	19
F+G	45	11	2	19	2	10	6	1	4	12	5	15
C+F	29	11	...	15	12	2	69	42	3	29	25	40
C+F+G	12	2	...	3	2	3	2	...	1	1	1	10
B+F+G	1	...	...	...	...	2	...	...	1	...	...	8
Rest	16	3	1	1	...	1	8	4	1	15	2	13
Total	116	41	5	58	29	19	149	97	12	79	73	117

Key for symbols in composition groups as for Table V.

Composition of Stones in relation to their Site in the Urinary Tract and the Age and Sex of the Patient

The distribution of the calculi according to their composition group, site in the urinary tract and the age and sex of the patient is shown in Table VII. Because of the small number in some groups, only the 4 composition types—F, C, F+G and C+F—were compared, and bladder stones had also to be excluded except for males in the older age-group. Comparison of the proportions of patients with each of the composition types was made for the following:

1. Kidney stones from male and female patients aged 21 to 49 years. Highly significant ($P<0{\cdot}001$).
2. Kidney stones from male and female patients 50 years of age and over. Not significant ($P>0{\cdot}05$).
3. Ureteric stones from male and female patients aged 21 to 49 years. Highly significant ($P<0{\cdot}001$).
4. Ureteric stones from male and female patients 50 years of age and over. Not significant ($P>0{\cdot}05$).
5. Females with kidney stones in the 2 age-groups. Significant ($P<0{\cdot}02$).
6. Females with ureteric stones in the 2 age-groups. Significant ($P<0{\cdot}05$).
7. Males with kidney stones in the 2 age-groups. Significant ($P<0{\cdot}01$).
8. Males with ureteric stones in the 2 age-groups. Not significant ($P>0{\cdot}05$).
9. Females aged 21 to 49 years, kidney with ureter. Significant ($P<0{\cdot}01$).
10. Females aged 50 years and over, kidney with ureter. Not significant ($P>0{\cdot}05$).
11. Males aged 21 to 49 years, kidney with ureter. Not significant ($P>0{\cdot}05$).
12. Males aged 50 years and over, kidney with ureter. Significant ($P<0{\cdot}05$).
13. Males aged 50 years and over, bladder with kidney. Not significant ($P>0{\cdot}05$).
14. Males aged 50 years and over, bladder with ureter. Highly significant ($P<0{\cdot}001$).

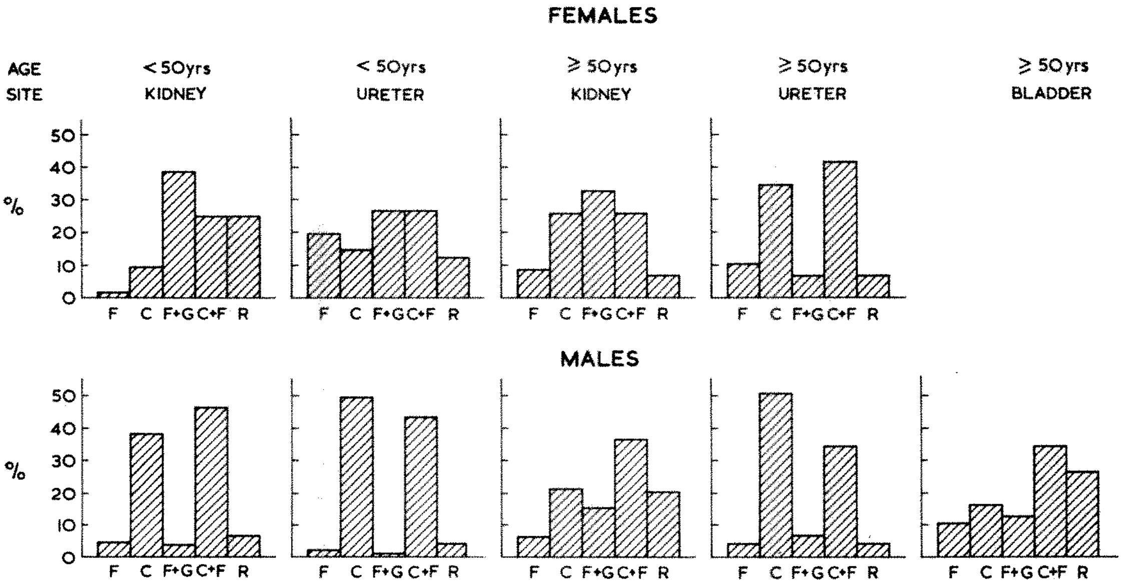

Figure. Percentage number of stones classified according to their composition group, site in the urinary tract and the patient's age and sex.

Key: C = calcium oxalate, F = calcium phosphate, G = struvite, R = remaining stones, *i.e.* those not belonging to one of the 4 main composition groups.

These differences in composition can be seen in the histograms of the Figure which give the percentages of each of the 4 main composition types and of the remaining stones for the subdivisions chosen. Only for kidney stones from females aged 21 to 49 years and males over 49 years, and for bladder calculi from the older males do the stones not belonging to one of the 4 main groups constitute a significant proportion of the total number of calculi.

The composition of urinary stones is related then to many variables. The largest differences in the distribution of stone type are a result of the effect of the patient's sex and are between males and females aged 21 to 49 years with kidney stones, and between those in the same age-group with ureteric calculi. For both sites, a higher proportion of men have C and C+F stones, while a higher proportion of women form F+G calculi (Figure). The differences between men and women for both sites are no longer significant in the older age-group, but nevertheless there is still a suggestion of more F+G kidney stones in women and C ureteric ones in men.

The effect of age on the distribution of the composition types is significant for men and women with kidney stones, the proportion of women with F and C varieties increasing and the proportion with F+G decreasing with age, while the proportion of men with C and C+F stones decreases and the proportion with F+G increases. There is a similar pattern for the ureteric calculi in that the proportion of females with C and C+F calculi increases and the proportion with F and F+G stones decreases with age, but the differences are not significant for the males.

The effect of site on the stone composition is not as large as that of age and sex. There is a greater proportion of F+G stones in the kidney and F ones in the ureter for females in the younger age-group but the differences in the distribution are not significant for the older group although there is a tendency towards more of the F+G variety in the kidney. There is no difference in the composition of kidney and ureteric stones from males aged 21 to 49 years but in the older group there is a greater proportion of F+G stones in the kidney and C stones in the ureter. For this male age-group the distribution of composition types in the bladder is the same as in the kidney, but the distributions for ureteric and bladder stones differ significantly ($P<0{\cdot}001$), there being a much greater proportion of C stones in the ureter.

Mean Weight of Stones classified according to their Composition Group, Site in the Urinary Tract, and the Age and Sex of the Patient

The average weight of the stones in the various subdivisions, the standard error of the mean and the number in each group are given in Table VIII. Using the logarithm of the weight instead of the actual weight because of the wide range of values encountered, an analysis of variance was performed on these data for kidney and ureteric calculi from males and females in the 2 age-groups. This indicated that the weight of a stone is affected by the different variables in the following way:

Age. Older people tend to have heavier stones which may, of course, result from the stones being present for a longer period of time.

Composition Type of Stone. The heaviest stones are the F+G ones followed by those of type F. Both the C and C+F varieties are much lighter.

Sex. When all composition types are considered together, men tend to have lighter stones but this sex effect varies according to the composition of the stone.

Site of Stone in Urinary Tract. Kidney stones tend to be heavier than ureteric ones but there is a suggestion that this effect may also vary with the composition type. However, this could well result from one exceptionally large ureteric stone of type F formed by a female in the older age-group.

In general, bladder calculi tend to be heavier than kidney and ureteric ones, though some kidney stones containing F+G are heavier. Again the C and C+F stones are lighter than other varieties.

Number of Stones

Further subdivision of the main data to show the number of cases of single and multiple calculi for the usual divisions of sex, age, site and composition type was not practical because, as already noted, there are many more examples of single stones than multiple ones. The distribution of single and multiple stones in the 3 sites shows a higher proportion of single calculi in the ureters and of multiple ones in the bladder. There is also a tendency for C stones to be single. Graphs of the mean of the total weight of stones formed by a patient against the number of calculi for the different composition types show that multiple calculi may be heavier or lighter than a single stone of the same composition. However, when all types are grouped together the mean weight of a single stone is always less than the mean weight of material from patients with 2, 3, 4, etc., calculi.

Table VIII

Mean Weight (g), Standard Error of the Mean and Number of Observations (in brackets) for the Stones divided according to their Composition Group and Site in the Urinary Tract and the Patient's Age and Sex

Sex	Female			
Age (years)	21-49		50 and over	
Site	Kidney	Ureter	Kidney	Ureter
Composition group				
F	0·90 ± 0 (2)	0·73 ± 0·26 (8)	3·82 ± 1·75 (5)	10·30* ± 9·82 (3)
C	0·72 ± 0·44 (11)	0·10 ± 0·04 (6)	1·37 ± 0·41 (15)	0·24 ± 0·05 (10)
F+G	5·31 ± 1·46 (44)	0·66 ± 0·25 (11)	8·94 ± 2·39 (17)	2·05 ± 1·95 (2)
C+F	1·39 ± 0·44 (28)	0·25 ± 0·07 (11)	3·24 ± 1·46 (15)	0·78 ± 0·39 (12)
C+F+G	6·62 ± 4·00 (12)	0·15 ± 0·05 (2)	17·83 ± 16·20 (3)	0·35 ± 0·25 (2)
B+F+G	6·00 ... (1)	...	...	...

Sex	Male				
Age (years)	21-49		50 and over		
Site	Kidney	Ureter	Kidney	Ureter	Bladder
Composition group					
F	5·92 ± 4·17 (7)	0·08 ± 0·02 (2)	3·64 ± 1·84 (5)	0·43 ± 0·18 (3)	11·07 ± 6·12 (11)
C	0·57 ± 0·21 (57)	0·10 ± 0·01 (48)	0·92 ± 0·61 (16)	0·20 ± 0·04 (37)	3·48 ± 0·67 (19)
F+G	4·37 ± 1·58 (6)	0·40 ... (1)	11·60 ± 5·49 (12)	1·38 ± 0·66 (5)	7·38 ± 1·73 (14)
C+F	1·49 ± 0·44 (69)	0·15 ± 0·02 (42)	3·28 ± 1·10 (29)	0·23 ± 0·33 (24)	5·11 ± 1·65 (39)
C+F+G	5·00 ± 3·02 (2)	...	7·00 ... (1)	0·40 ... (1)	16·31 ± 6.26 (9)
B+F+G	...	...	...	...	22·03 ± 9·73 (8)

Key for symbols in composition groups as for Table V.

* This large mean results from 1 unusual stone which had grown to almost fill 1 ureter and was long and tubular in shape.

Stone Formation in relation to Occupation

The patient's occupation was provided in only 476 cases and this figure includes 136 housewives. A further 31 persons who were known to be retired were excluded from the calculations since it could not be unambiguously determined whether the stone had started during retirement or employment. The amount of useful data for studying stone formation in relation to daily occupation was therefore limited. However, over the past 60 years, occupations have been arranged in 5 broad groups called Social Classes to assist in surveys like this one (Classification of Occupations, 1960). These groups are: I, Professional, etc. occupations; II, Intermediate occupations; III, Skilled occupations; IV, Partly skilled occupations; V, Unskillled occupations. The division is such that the occupations in each group have the same general standing in the community, and is therefore dependent on factors like education and economic environment but is not related to the average salary in the various occupations. Social Class I is wholly "non-manual", Social Class V wholly "manual" but Classes II, III and IV contain both types of workers appropriate to the class.

The 1961 Census figures for Great Britain and Northern Ireland are the latest available giving details of occupations in the population. From these the number of "economically active" persons over 15 years of age in each group who were employed at the time of the Census was calculated. Those unemployed had to be excluded since their occupations were omitted from the tables. "Economically inactive" persons such as inmates of establishments, students, retired workers and a large proportion of the female population which would include the housewives are not assigned to a Social Class.

Table IX

Comparison of the Relative Frequency of Urolithiasis, by the 5 Social Classes (see text), for 340 Patients

Social Class Group	A (%)	B	C	D	E
I	2·89	9·8	19	1·94	10·8
II	15·29	52·0	83	1·60	8·9
III	50·64	172·2	155	0·90	5·0
IV	22·88	77·8	78	1·00	5·6
V	8·09	27·5	5	0·18	1·0
Not classified	0·21	0·7	...	...	...

A: percentage frequency of Social Class group in the "economically active" population (23,273,353 persons).
B: expected frequency of urolithiasis amongst 340 patients assuming equal liability to the disease.
C: actual frequency found.
D: ratio C/B.
E: frequency normalised to Social Class V.

The actual number of stone cases in each group and the expected number for 340 cases assuming an equal liability of the population to the disease are shown in Table IX. There is a definite correlation between stone formation and occupation and, in general, the incidence of urolithiasis decreases as the Social Class group changes from I to V. A professional worker such as a doctor has 10 times the chance of developing the disease compared with an unskilled worker like a labourer. Whether this difference in incidence is related to diet, physical activity, etc. has yet to be proved. Mates and Křížek (1958) in their Czechoslovakian clinic found that the stone incidence decreased for the following order of occupations: health workers, administrative workers, unclassified, manual workers and agricultural workers. The results from the 2 studies are in accordance since health and administrative workers would be classified by our system as Social Class I or II and manual and agricultural workers would belong in Classes IV or V.

The 136 housewives constitute 28·5% of the stone-formers with details of occupation. In the group of "economically inactive" persons are just over 12 million females comprising 30·0% of the total population, most of whom are likely to be housewives. A rough comparison between the 2 groups should therefore be possible. The incidence of housewives among stone-formers is slightly less than their incidence in the whole population. Such an occupation is not then at risk with regard to stone formation and in this respect it is equivalent to Social Class groups III and IV.

The number of known occupations is too small for the groups to be subdivided according to the age and sex of the patient and the composition, site and weight of the stone. What is, however, noteworthy is that patients of known occupation with uric acid and uric acid-containing stones belong mainly in Social Class group I and to a lesser extent in groups II and III.

Composition of the Nucleus compared with the Rest of the Stone

Only calculi possessing a laminated structure or some definite arrangement of material could be used to compare the composition of the nucleus, or the interior when these areas were homogeneous and could not be separated, with that of the rest of the stone. This meant excluding many small upper urinary tract calculi consisting of aggregates of crystalline material of various textures which had to be sampled as a whole. The results therefore do not represent the nucleus composition for this collection, but nevertheless they show any differences in the occurrence of constituents in various stone areas. Table X presents the weighted percentage composition of the relevant areas for stones from the upper and lower urinary tracts; no further subdivisions were made. Calcium oxalate monohydrate occurs in larger amounts in the nuclei, whereas the dihydrate is found in greater quantities in the outer areas of stones from both sites. Hydroxyapatite is more abundant in the nuclei of upper urinary tract stones but is evenly distributed in the lower tract ones. Both carbonate-apatite and struvite show no variation in composition in either site. Observations on the minor constituents may not be significant since the numbers involved are small but the trends observed are as follows. Whitlockite and ammonium acid urate occur in slightly greater quantities in the nuclei, and brushite and octacalcium phosphate are more abundant in the outer areas. No definite pattern emerges for the uric acids. They are more frequent constituents of the outer areas except in the case of uric acid dihydrate in lower urinary tract stones.

Table X

Weighted Percentage Composition of Nucleus and of Rest of Stone for Calculi with Observable Nuclei or with Homogeneous Nuclear and Interior Regions

	Constituent															
Stone Area	A1	A2	B	J	C1	C2	D	F1	F2	F3	F4	F5	G1	G2	X	H
(a) *402 upper urinary tract stones*																
Nucleus	0·9	0·1	0·5	0·2	28·9	11·0	1·9	24·7	15·0	0·8	2·1	0·2	0·1	13·4	0·1	0·1
Rest	1·1	0·3	0·1	...	19·8	23·7	1·8	25·4	11·8	1·3	1·4	0·4	0·2	12·2	0·1	0·4
(b) *123 lower urinary tract stones*																
Nucleus	2·2	2·5	1·8	0·1	27·8	6·3	1·6	21·1	11·4	1·2	2·6	0·9	...	18·1	...	2·4
Rest	3·1	1·2	1·2	0·1	19·8	14·7	1·6	24·0	10·7	1·5	1·2	1·7	0·3	18·9	...	...

See Table I for explanation of symbols.

Summary

In a collection of 856 urinary calculi from Great Britain and Northern Ireland, the most abundant and frequently occurring crystalline constituents are the mono- and di-hydrates of calcium oxalate and hydroxy- and carbonate-apatite.

On the basis of composition, most stones can be assigned to a few well-defined groups. The most common composition type, accounting for 34% of the collection, is that composed of calcium oxalate+calcium phosphate. The oxalate can be either or both of the hydrates, often both are present, but the calcium phosphate is generally hydroxyapatite. Stones consisting of pure calcium oxalate make up 27% of the total, while those comprised of struvite+calcium phosphate contribute 17%. In the latter variety the calcium phosphate is almost invariably carbonate-apatite. The other group considered consists of the pure calcium phosphate calculi which account for 7% of the collection.

The incidence of stones in relation to their site in the urinary tract and the patient's age and sex has been investigated, together with the effect of the stone site, patient's age and sex on the distribution of calculi in the main composition groups and the effect of composition, site, age and sex on the stone weight. Most of these variables have a significant effect on one another.

The incidence of stones is also related to daily occupation, professional workers being 10 times more likely to develop urolithiasis than labourers.

We thank the Medical Research Council and Nuffield Foundation who financed most of this work and Mr D. Sturt who kindly agreed to the participation of the Computer Centre in this project. We are greatly indebted to Mr N. W. Please for advice and many helpful discussions on the statistics and for carrying out the analysis of variance. Finally, we are grateful to the many surgeons and physicians who provided the stones and the data.

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High-Dose Delayed Urogram in the Detection of the Occult Ectopic Ureter

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Ureteral ectopy is occasionally difficult to diagnose since the symptoms are variable in nature and may be delayed in onset, conventional radiology being misleading.

The difficulties are illustrated in 4 patients presenting recently at the United Norwich Hospitals. The diagnosis in these patients has been made more easily by using simple modifications of standard radiological techniques, described later.

All the patients were girls, in whom this anomaly is more common (Malek *et al.*, 1972). The first shows a classical presentation, the second is less usual and the last 2 are exceptional but have similar features.

Case Reports

Case 1 (Left complete duplication with ectopy)
Miss J. R. had been incontinent of urine since birth, dribbling between bouts of normal micturition and she was occasionally enuretic. When examined at the age of 5 years her vulva was wet but her urine culture was sterile. The original excretion urogram showed an enlarged left upper renal pole, and a high-dose urogram, done subsequently, showed contrast gathering slowly at this site (Fig. 1). Normal ureteric orifices were found on cystoscopy but a small cystic swelling was seen in the anterior vaginal wall, from the region of which urine trickled although no actual opening was visible.

Exploration of the left kidney revealed a cystic upper pole draining into a greatly dilated pelvis and ureter. The abnormal ureter was traced down to the pelvic brim and was excised together with the cystic upper pole, preserving the healthy kidney and normal ureter and thus curing her urinary incontinence.

This common presentation produces no great diagnostic difficulty but the situation may be far from straightforward, however, as will be shown.

Case 2 (Left complete duplication with ectopy)
Miss B. G. had a first attack of pyelonephritis at the age of 3 months. Following a normal excretion urogram 2 years later chemotherapy was maintained almost continually until the age of 11 years. In 1966, at the age of 14 years, recurring attacks of left loin pain each lasting 2 weeks, led to a further excretion urogram and a micturating cystogram, both of which were thought at the time to be normal. The appearance of the cystogram is shown in Figure 2. No abnormality was found on endoscopic examination.

As a student aged 19 years she complained of persistent left loin pain, relieved by intermittent leakage of urine. A further urogram showed distortion of the left upper renal pole and a micturating cystogram showed a possible urethral diverticulum, the appearance being very similar to that produced by the original cystogram in 1966.

A high-dose delayed urogram initially showed a lateral displacement of the "normal" ureter on that side (Fig. 3), implying the presence of a dilated ectopic ureter (Amar, 1971) and later the abnormal left upper renal pole was displayed (Fig. 4).

The urethral opening of the "diverticulum" was found under anaesthesia and contrast injected into it revealed a dilated ectopic left ureter and grossly hydronephrotic left upper renal pole.

Exploration of the left kidney revealed a sac-like upper pole, separated by a groove from normal cortex, from which it was excised.

The dilated ectopic ureter was ligated and divided in the pelvis. Her postoperative progress was satisfactory and she has since been dry and free from pain.

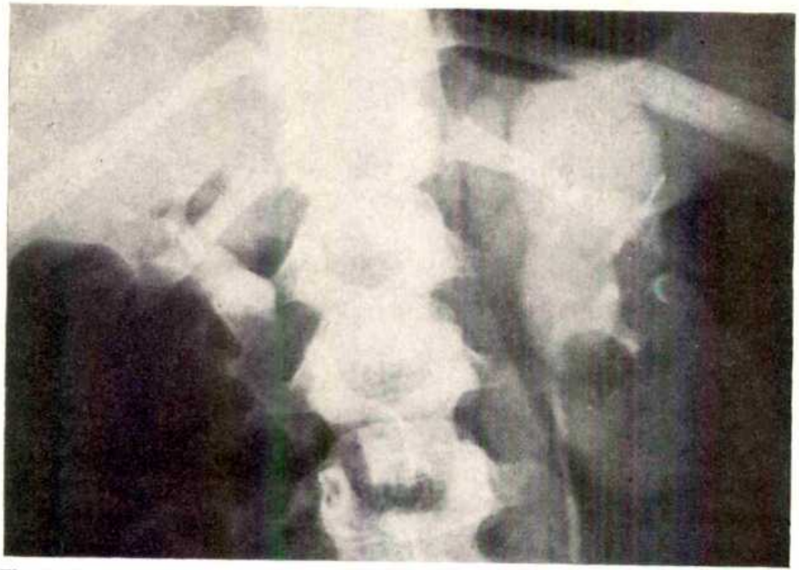


Fig. 1. Case 1 (J. R.). Sac-like left upper renal pole shown with a high dose of Conray after a delay of 3 hours.

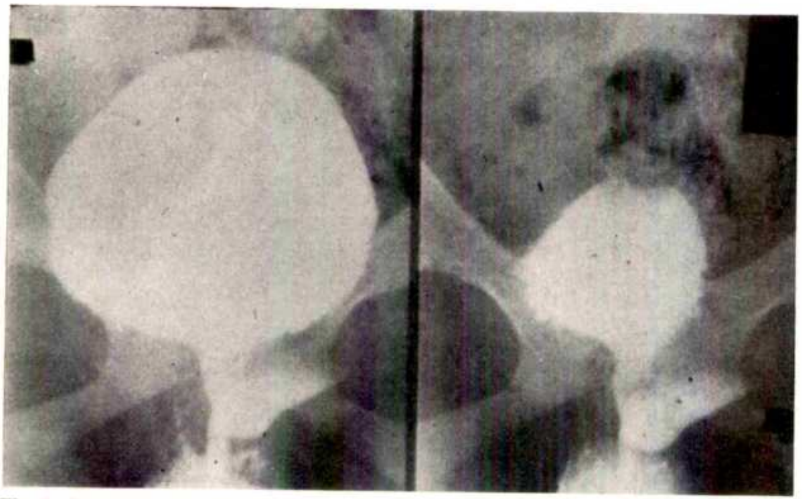


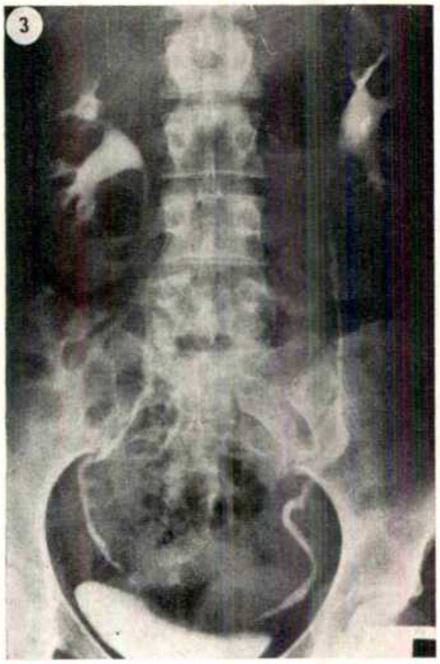
Fig. 2. Case 2 (B. G.). Contrast filling an area to the left of the urethra on a micturating cystogram done in 1966.

The last 2 patients were of great interest owing to the similarity of their abnormality and clinical presentation.

Case 3 (Bilateral complete duplication with bilateral ectopy)

Miss L. D. had been incontinent of urine since birth. At the age of 6 years she underwent removal of the upper part of a left duplex renal system, the ectopic ureter being traced to its urethral opening and ligated.

In 1969, at the age of 15 years, she was seen here because of continuing dribbling of urine which occurred more particularly on stress. This leakage was at first blamed on some abnormality of the intrinsic urethral mechanisms. Pelvic exercises had produced no benefit over previous years and she had resorted to wearing vulval pads whilst at boarding school. Examination was normal but her urine was infected with coliform organisms.



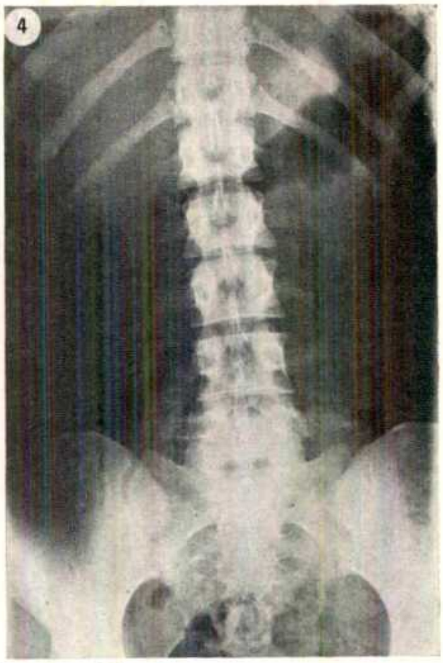


Fig. 3. Case 2 (B. G.). Lateral displacement of the normal left ureter.

Fig. 4. Case 2. (B. G.). Opacification of the left upper renal pole after a long period of delay.

An excretion urogram was said to be normal and under an anaesthetic a mid-urethral stricture of 8 Fr. diameter was found and dilated. Cystourethroscopy then showed a normal trigone and ureteric orifices and there was no hint of an ectopic opening. Indigo-carmine injected intravenously clearly emerged from both ureteric orifices and a pad placed on the vulva soon became soaked with clear fluid.

A high-dose urogram, viewed under an image intensifier after a period of 4 hours produced the appearance shown on Figure 5.

Subsequent exploration of the right side confirmed the presence of a second duplex system, and the ectopic renal segment and ureter were removed down to the level of the paraurethral tissues. This procedure has left her dry.

Case 4 (Bilateral complete duplication with bilateral ectopy)
Miss V. J. had also dribbled from birth, between episodes of normal voiding. When she was 12 years of age an excretion urogram was reported as normal (Fig. 6). However, examination under anaesthesia in Leicester revealed a pit between urethra and vagina which, after dilatation, admitted a ureteric catheter. An injection of contrast demonstrated conclusively the presence of an ectopic right renal segment. This was excised by right upper pole partial nephrectomy and upper ureterectomy but she continued to dribble postoperatively. This leakage was presumed to be due to drainage from the ureteric stump. She was seen here at the age of 15 years with symptoms unchanged and a sterile urine.

Review of her previous urogram was possible and with hindsight a blob of contrast could be made out above and medial to the right kidney, representing the lesion already treated.

Furthermore, there seemed to be some opacification in an equivalent position above the *left* kidney. Films done with a high dose of contrast demonstrated a definite left-sided opacity above an otherwise normal looking left kidney (Fig. 7).

Examination was repeated under anaesthesia and a septate vagina was found. A left-sided vagino-urethral pit was seen with some difficulty and, using an acorn-ended catheter, injected contrast outlined a further ectopic ureter. This was subsequently excised with its attached renal segment and she has since been dry.

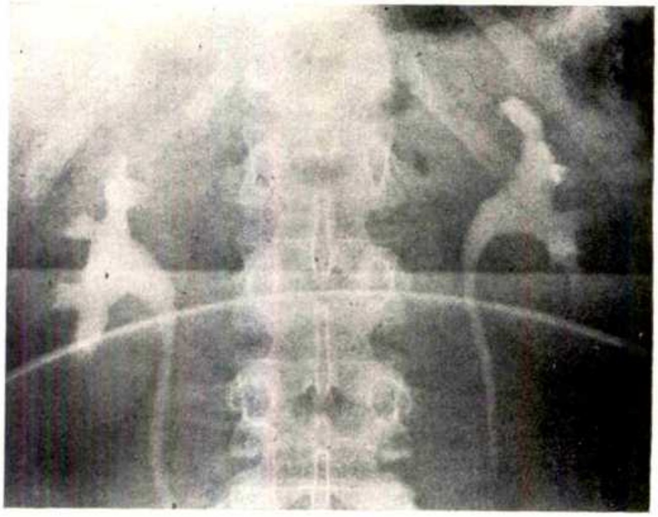


Fig. 6. Case 4. (V. J.) Standard excretion urogram showing blobs of contrast above and medial to the upper calyces of both kidneys, in the line of the 12th ribs.

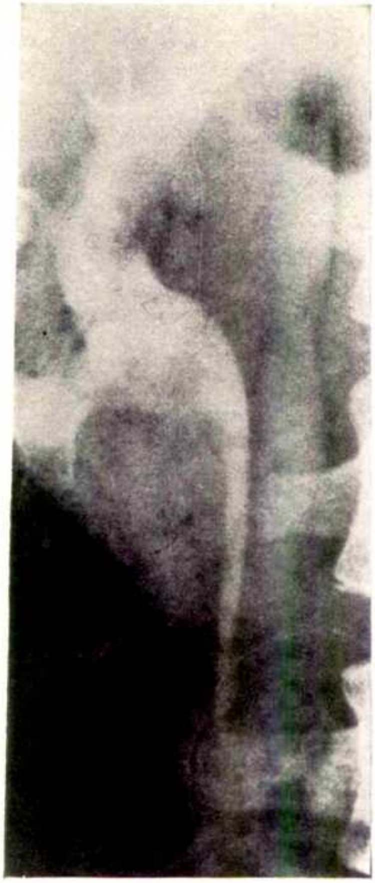


Fig. 5. Case 3 (L. D.). Delayed opacification of a right ectopic ureter medial to the normal ureter.

Comment

A straightforward history of urinary incontinence from an early age, between episodes of normal voiding, may lead to an out-patient diagnosis of ectopic ureter in many patients but in some the answer may not be so easily obtained. For example, although 3 of our 4 patients had dribbled urine since birth a diagnosis was not made in 1 patient until the age of 19 years and 2 others had their second ectopic segments detected at the age of 15 years, 1 having first presented at the age of 12.

Little may be found on examination. A wet vulva may be present but a loin mass is unusual (Malek *et al.*, 1972). Pressure over such a mass has produced turbid material at the vulva from an ectopic ureter (Johnston and Davenport, 1969) but this is exceptional.

The urine is said frequently to be infected but only 1 of our 4 patients had bacteriuria on presentation. An excretory urogram may contribute to the diagnosis at an early stage but the signs may be indirect because the renal segment drained by the ectopic ureter tends to secrete contrast very slowly and to concentrate it poorly.

The "drooping flower" appearance is typical but not invariable (Parker, Pohl and Robison, 1970); it was seen in 1 of the 6 ectopic renal segments discussed here. Amar (1971) has described lateral displacement of the ureter draining the "normal" renal segment, particularly at its lower part, by a non-visualised ectopic ureter, and this sign was certainly seen on the third urogram of one of our patients.

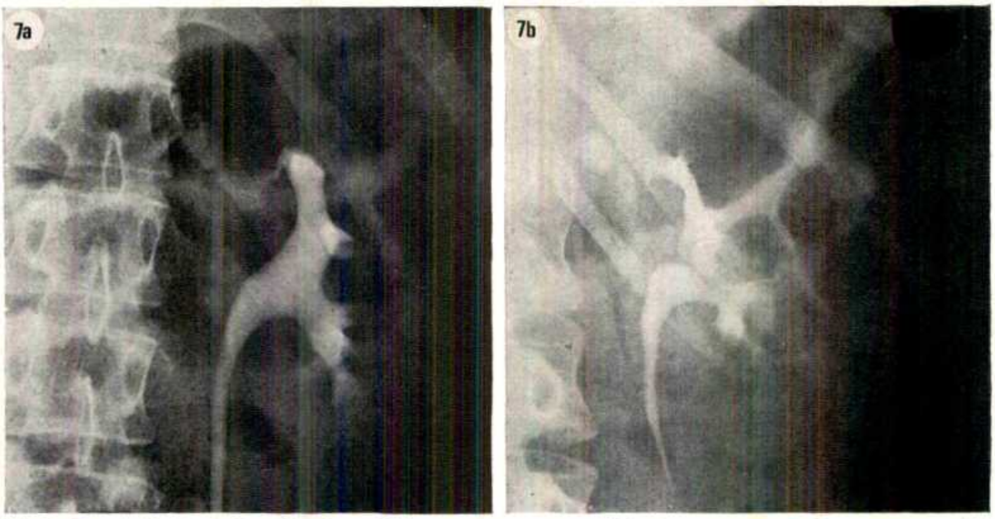


Fig. 7. Case 4 (V. J.). **A,** Opacification of left upper segment on high-dose urogram. **B,** Same urogram with slight rotation of the patient. Showing contrast areas overlying 12th rib in **A.**

Other inconstant signs have been described, such as widening of the area between the upper renal outline and the uppermost secreting calyx (Crenshaw and Buchtel, 1936) and lateral displacement of the normally secreting renal segment may occur.

Retrograde ureteropyelograms of the abnormal ureters were of value in 2 of the 4 patients and in 3 of the 6 kidneys shown here to have ectopic segments.

However, a micturating cystogram revealed the site of the ectopic opening in 1 patient, while a difficult re-examination under anaesthesia after a delay of 3 years was required to locate the second opening in another. Thus, only 1 of 6 ectopic ureteric openings was detected without some difficulty or delay.

Clearly, direct visualisation of an ectopic segment without instrumentation is preferable and this is possible using the high-dose delayed urogram. In each of our patients 100 ml of "Conray 325" was given intravenously and the period of the delay varied from 3 to 24 hours. At intervals the renal areas of patients were observed using an image intensifier and films were taken when contrast could be seen.

In 5 of 6 abnormal kidneys the ectopic segment eventually secreted and concentrated enough contrast for adequate demonstration on conventional radiology without tomograms.

It is of interest that ureteropyelograms, with injection of contrast into an ectopic opening, produced an increase in size of ectopic renal segments compared with their appearance on delayed urograms. This may indicate distensibility of the segments and their optimal appearance on urography may, therefore, depend on their degree of filling. If the secretion and discharge of a segment is intermittent it may even be missed on single films taken at intervals during a delayed urogram, confirming the value of the image intensifier.

There is an unfortunate superimposition, from the radiological point of view, of the upper renal pole on the 12th rib and a faint blob of poorly concentrated contrast may blend with the bony texture of the rib. This appearance certainly led to delay in diagnosis in 1 of our patients (Fig. 7).

It should be remembered that if the condition is bilateral, as in 2 of our patients, and one side only is found first, then it is likely that the side detected is that which is automatically more prominent and functionally more active. A more obvious urographic abnormality would therefore be produced. After treatment of the more active segment the symptoms may largely, but not completely, be relieved. Thus it is tempting, with minimal symptoms of vulval wetness, to blame abnormal urethral mechanisms, persisting infection or drainage from the remaining ureteric stump (Malek *et al.*, 1971). Suspicion of a further lesion may therefore be suppressed and this occurred in our last 2 patients. It may be necessary to redouble efforts in the patient with minimal symptoms of incontinence and a normal trigone (Cox and Hutch, 1966) to exclude a contralateral ectopic segment. A most valuable means of doing so, even in the presence of a poorly secreting segment, appears to be the high-dose delayed urogram, used with the image intensifier.

Summary

Two cases of unilateral and 2 of bilateral ureteral duplication with ectopy are presented.

Five of 6 ectopic renal segments were visualised directly without instrumentation by means of high-dose urograms with delayed films. This technique is recommended in the investigation of possible ureteral ectopy.

We are grateful to Mr Guy Baines of Birmingham for referring Case 2 and also to Mr J. Gordon Smart of Leicester for the loan of radiographs in Case 4.

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Simplified Cystography in Stress Urinary Incontinence

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It is evident from our extensive physiological studies of the normal and the incontinent urinary sphincter that in true primary stress incontinence there is no intrinsic damage to the various elements of the sphincteric mechanism. Rather, it is the loss of the support of the vesico-urethral junction that is responsible for the loss of the efficiency of an otherwise intact sphincteric mechanism. This loss of support is also the primary factor responsible for the vesico-urethral anatomic changes seen cystographically. Traditionally, more emphasis has been given to these secondary anatomic changes than to the primary factor responsible for them. In the study of stress incontinence, a simple cystographic examination of the type presented herein provides the information needed to assist diagnosis, assess prognosis and define the aim of surgical correction.

Material and Method

Determination of the resting location of the vesico-urethral segment in relation to the pubic bone and the degree of its mobility both downward and posteriorly is the object of this cystographic examination.

The patient lying supine on the X-ray table, the bladder is filled by gravity to capacity with radiopaque solution through a 16 F, soft rubber catheter. Anterior and oblique views are obtained. Then, the patient still lying on the table and the catheter still in place, 2 absolute lateral exposures are taken, the first with the patient relaxed and the second with maximum straining. One should be able to overlap the bony structures of these 2 exposures. The catheter is now removed and a voiding film in oblique position is obtained.

The catheter filled with radiopaque material helps to delineate the urethra clearly. Its meeting with the base of the bladder defines the vesico-urethral segment. The distance from any radiographically clear fixed bony point, such as the pubic foramen, ischial spine, ischial tuberosity, etc. to the posterior vesico-urethral angle is measured and the degree of vesico-urethral displacement with straining can easily be determined.

25 women with known normal urinary control on whom cystography was done for some other reason were examined according to the previously outlined technique. They were considered a control group representative of women with normal continent vesico-urethral segment. Ages varied from 17 to 65 years.

48 women with stress urinary incontinence were also examined. Ages in this group were mainly between 45 and 72; 2 patients were in their late teens and 1 was 23 years of age. These patients could be divided into 2 main groups: (1) those with pure stress incontinence who had not been operated upon before and (2) those who had had unsuccessful surgical repair, either immediate postoperative failure or failure after a temporarily successful result.

Findings

The vesico-urethral junction in normal, continent women is located opposite the lower third of the pubic bone. A line dropped perpendicularly from the anterior vesico-urethral angle over the

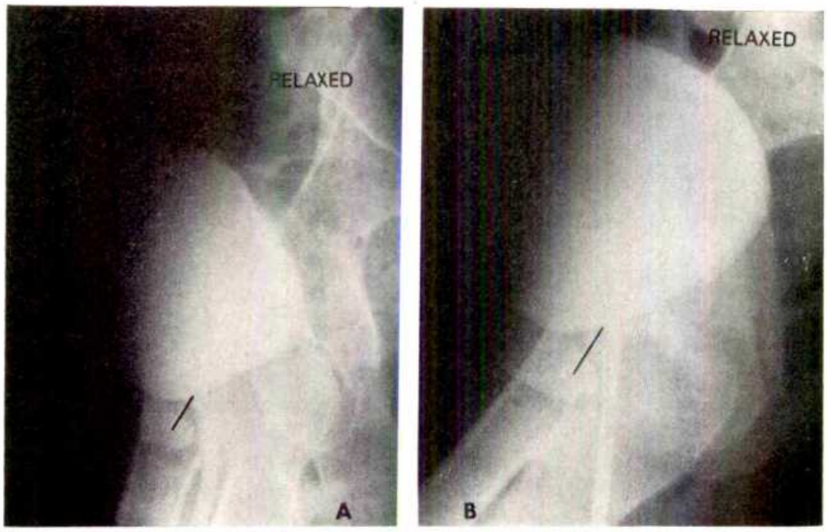

Fig. 1. Lateral cystograms of 2 continent women in relaxed state. Perpendicular line from anterior vesico-urethral angle over the long axis of pubic bone crosses latter near junction of middle and lower thirds.

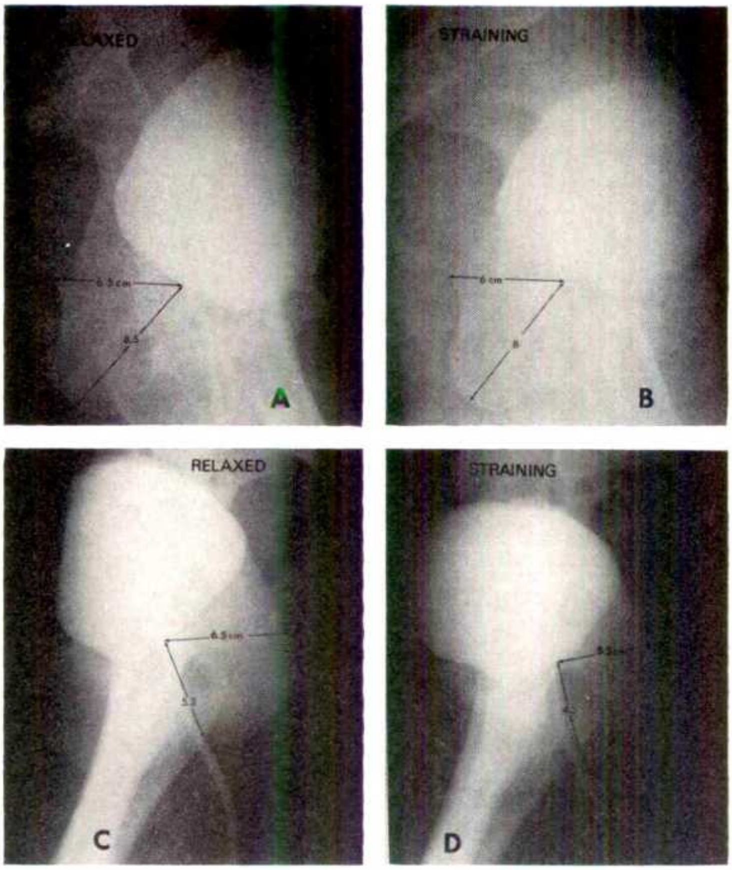

Fig. 2. Lateral cystograms of 2 young, continent women. **A**, 28-year-old woman in relaxed state. **B**, With straining, vesico-urethral segment displaced 0·5 cm downward and posteriorly. **C**, 34-year-old woman in relaxed state. **D**, With straining vesico-urethral segment displaced 0·8 cm downward and 1 cm posteriorly.

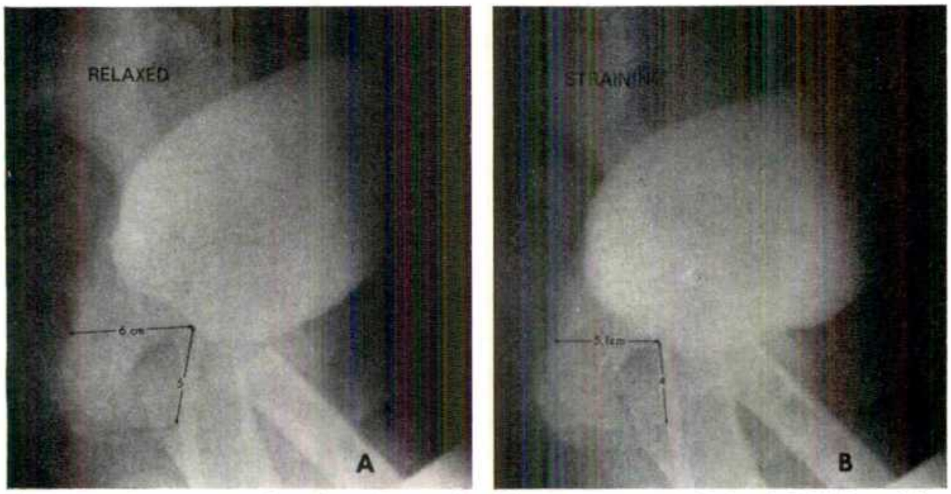

Fig. 3. Lateral cystograms of continent 55-year-old nulliparous woman. **A**, Relaxed. **B**, With straining, vesico-urethral segment displaced 1 cm downward and 0·9 cm posteriorly.

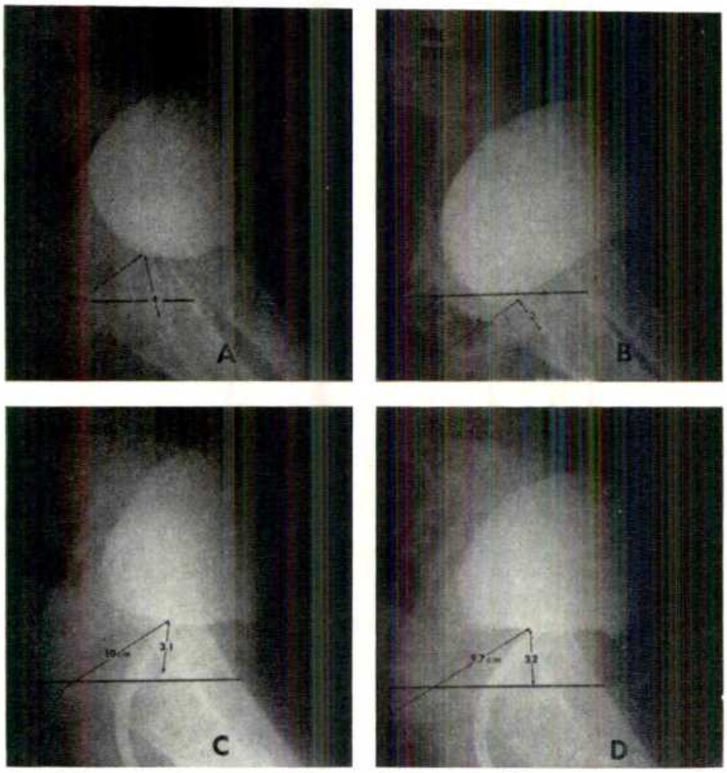

Fig. 4. Lateral cystograms of 58-year-old woman with moderate stress incontinence. **A**, Preoperative, relaxed. Note slightly low position of vesico-urethral junction. Wide posterior vesico-urethral angle. **B**, With straining, vesico-urethral segment displaced 2 cm downward and 3 cm posteriorly. Posterior vesico-urethral angle improved. **C**, Postoperative relaxed. Note effect of proper suspension and support of vesico-urethral segment. **D** Shows limited mobility of vesico-urethral segment (0·1 cm downward and 0·3 cm posteriorly) after successful repair.

long axis of the pubic bone will cross the latter at about the junction of its middle and lower thirds (Fig. 1). With straining, the vesico-urethral segment moves posteriorly and downward 0·5 to 1·5 cm, depending on the age of the patient and the integrity of the pelvic floor.

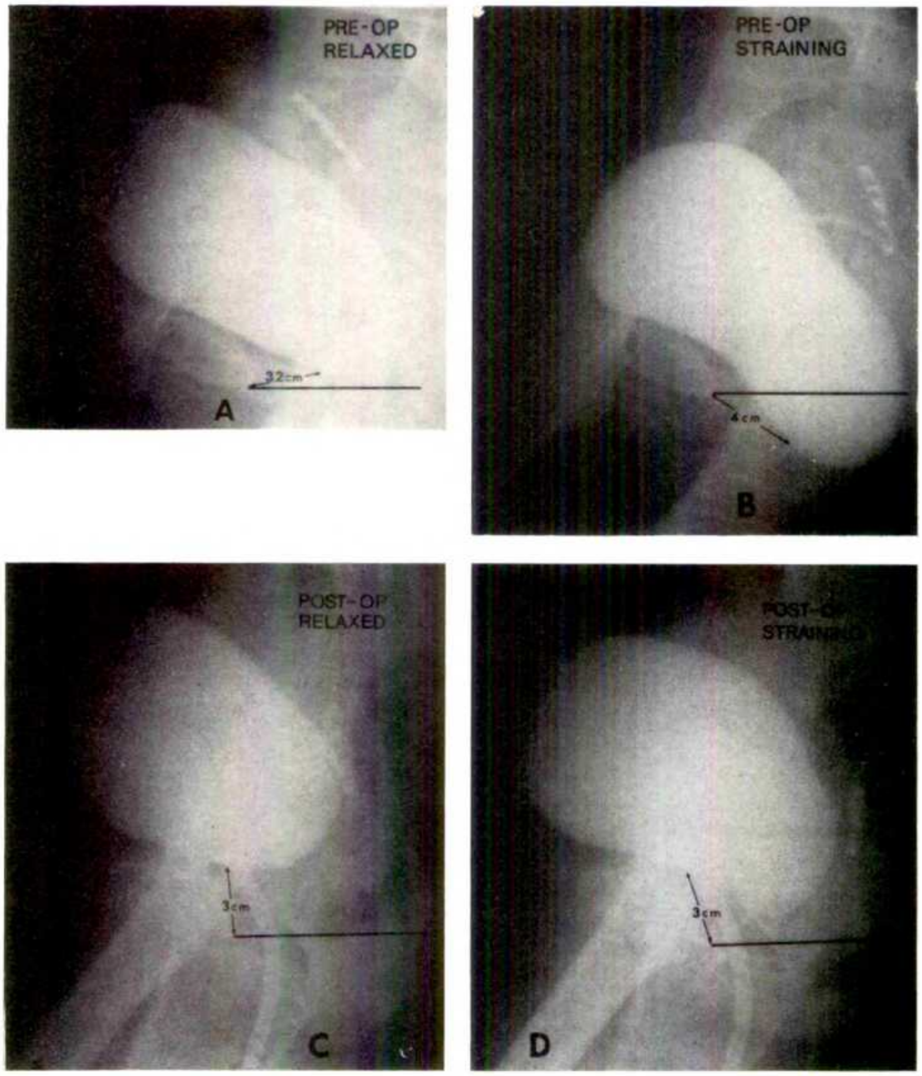

Fig. 5. Lateral cystograms of 43-year-old woman with marked stress incontinence and appreciable uterine prolapse. Horizontal line at inferior pubic margin demonstrates extent of downward mobility. **A**, Preoperative, relaxed. Note low-lying vesico-urethral junction. Posterior vesico-urethral angle near normal. **B**, With straining, excessive downward and posterior mobility of vesico-urethral segment is shown. Uterus (seen by intra-uterine device) also freely mobile. **C**, 6 months postoperative, relaxed. Note restoration of normal position of vesico-urethral segment (compare to **A**). **D**, With straining, vesico-urethral junction shows minimum mobility, with appreciable uterine mobility.

In physically active young women with an intact pelvic floor, the degree of vesico-urethral mobility is very limited—an average of 0·5 cm downward and posteriorly (Fig. 2). Elderly women with perfect urinary continence and control, yet with relatively weaker pelvic support, have a wider range of vesico-urethral mobility (up to 1·5 cm) (Fig. 3).

The patients with true stress incontinence who have had no previous surgery invariably show

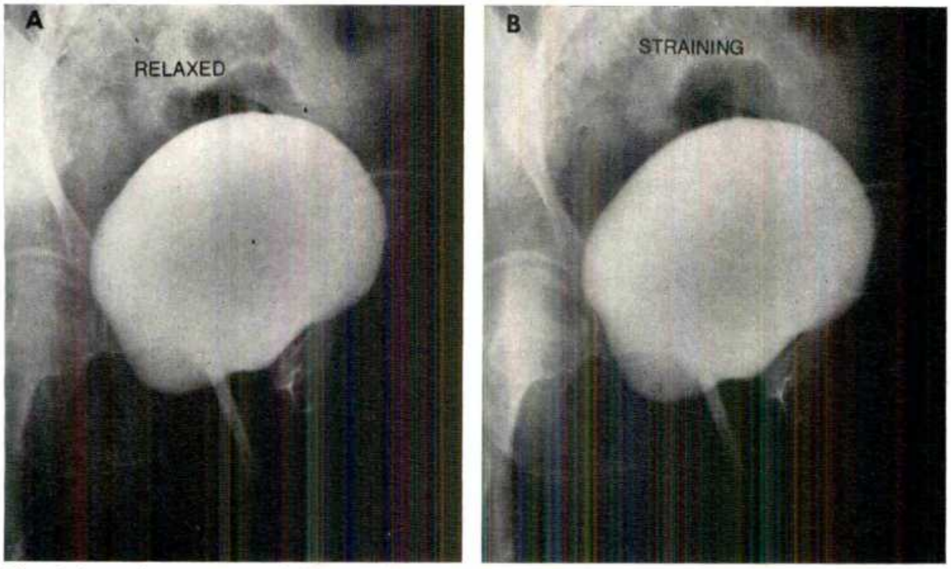

Fig. 6. Lateral cystograms of 55-year-old woman with severe stress incontinence after failure of 4 attempts (2 vaginal, 2 suprapubic) at surgical repair show absolute fixation of vesico-urethral segment. **A**, Relaxed. **B**, With straining.

excessive mobility of the vesico-urethral segment beyond the normal range. The initial resting position of the vesico-urethral segment is either normal or slightly lower and is not related to the degree of displacement with straining. The degree of mobility, however, seems usually to correlate with the degree of incontinence (Fig. 4).

Although variable degrees of uterine prolapse are frequently encountered (Fig. 5, A and B). abnormal mobility of the vesico-urethral segment is the factor responsible for the incontinence. Proper fixation and support of the vesico-urethral segment result in cure of the incontinence despite persistence of the uterine prolapse (Fig. 5, C and D).

Frequently associated with the abnormal mobility are changes in the posterior vesico-urethral angle. In some cases, however, the posterior vesico-urethral angle is within normal range (Fig. 5, A) or improves with straining despite the presence of excessive mobility and stress incontinence (Fig. 4, B).

Patients with persistent stress incontinence after unsuccessful surgical repair, especially suprapubic urethral suspension procedures, show 1 of 2 different pictures:

1. Absolute fixation of the vesico-urethral segment in an abnormal (usually lower and more posterior) position in reference to the pubic bone: this situation is found especially after repeated attempts at surgical repair, which result in excessive fibrosis and fixation of the entire segment in an abnormally low position (Fig. 6). Unless this fixation in an abnormal position is corrected, incontinence cannot be cured (Fig. 7).

2. Excessive mobility and abnormally low resting position of the vesico-urethral segment (Fig. 8); this group differs from the stress incontinence patients who have not undergone surgery in that the resting position of the vesico-urethral segment is abnormally low. The abnormal mobility may not be very pronounced in patients whose vesico-urethral segment is markedly displaced in the resting position. These patients are commonly those who have immediate postoperative failure, or failure after a short period of temporary success. It seems that after surgical freeing of the vesico-urethral segment, if the attempted support fails, this segment will sink freely downward and posteriorly even under resting conditions. In such cases incontinence is more marked than before the unsuccessful surgical attempt (Fig. 9).

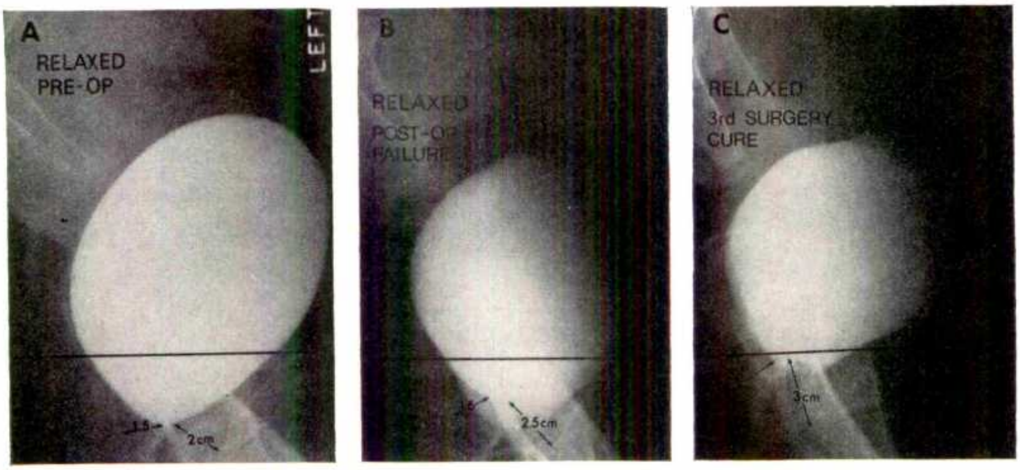

Fig. 7. Lateral cystograms of same patient as in Figure 6. Horizontal line at upper margin of pelvic bone shows relative position of vesico-urethral segment after each surgery. **A**, After failure of 2 vaginal and 1 suprapubic repairs. Note very low, dependent vesico-urethral junction. **B**, After failure of second suprapubic repair. Some improvement in position of vesico-urethral segment. **C**, 4 months after third and finally successful attempt at repair. Further improvement in position and support of vesico-urethral segment. Patient now completely continent.

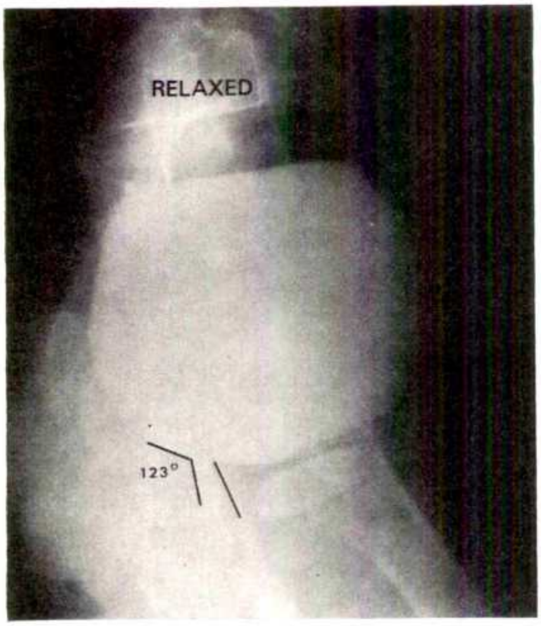

Fig. 8. Lateral cystogram of 54-year-old woman with stress incontinence 2 years after failure of 1 vaginal and 1 suprapubic attempt at repair. Note low resting position of vesico-urethral segment. Perpendicular line from anterior vesico-urethral angle over long axis of pubic attempt at repair. Note low resting position of vesico-urethral segment. Perpendicular line from anterior vesico-urethral angle over long axis of pubic bone crosses latter about 1·5 cm below its inferior margin. Slightly wide posterior vesico-urethral angle (123°).

Discussion

Diagnosis of stress urinary incontinence still remains primarily historical. A detailed history, with emphasis on the degree of incontinence, when it began, the time of leakage and its relation to associated activities and the state of bladder distension are helpful in separating true stress incontinence from other types of incontinence. Clinical examination, cysto-urethrography, endoscopy, cystometry and physiological sphincteric pressure studies are valuable confirmatory studies.

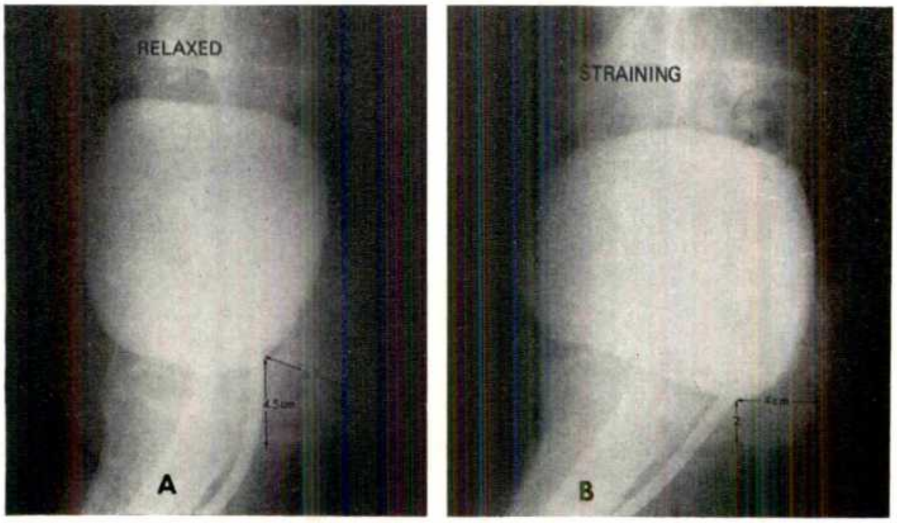

Fig. 9. Lateral cystograms of same patient as in Figure 8. **A**, Relaxed. Note low position of vesico-urethral junction. **B**, With straining, vesico-urethral segment displaced 2·5 cm downward and 2·2 cm posteriorly.

Cysto-urethrography is advocated by Millin and Read (1948), Ball (1950), Jeffcoate and Roberts (1952), Hodgkinson (1953, 1957, 1970), Roberts (1952, 1953) and Bailey (1956) as the most valuable diagnostic tool. Great importance has been ascribed to changes in the posterior vesico-urethral angle, the angle of inclination of the urethral axis (Green, 1962, 1968), the flatness of the bladder base and its relation to the pelvic outlet (Noll and Hutch, 1969). Several specific bony reference points have been chosen for the evaluation of one or other of the preceding features. Studies by Greenwald, Thornbury and Dunn (1967) and by Kitzmille, Manzer, Nebel and Lucas (1972) argue strongly against the validity of the radiologic signs and their correlation to stress incontinence or to cure. With critical analysis, it is evident that they are secondary features rather than primary causes of stress incontinence. Simple lateral cystographic studies in the relaxed and straining states demonstrate the primary defect of the weak pelvic support.

Surgically, whatever approach we use to repair stress incontinence, whether vaginal or suprapubic, we cannot improve the intrinsic structure of the sphincteric mechanism. We can correct only the abnormal position of the vesico-urethral segment and provide it with the proper support. Detailed pre- and postoperative sphincteric pressure studies have provided conclusive evidence that if the proper position and support of the vesico-urethral segment are achieved, the intrinsically intact sphincteric mechanism will do its job efficiently and maintain perfect continence (Tanagho, manuscript in preparation).

As long as the only thing we can offer surgically is to provide normal position and requisite support for the vesico-urethral segment, the cystographic study becomes essential, not so much for diagnosis as for prognosis. The vesico-urethral segment that is abnormally mobile or is fixed in an abnormal position is the one that can benefit from surgical repair and the aim of the repair should be to correct these defects.

To patients with stress incontinence whose vesico-urethral segment is in a normal position and exhibits a normal range of mobility, surgery can offer little except inducing mechanical obstruction by plication, compression or slings, none of which is really physiological. These patients usually have intrinsic sphincteric weakness, not uncommon after ill-advised and technically damaging surgical attempts. Another possibility is that further urological and physiological studies may reveal urge incontinence mistaken for stress incontinence.

It should be emphasised that cystography is not the means of diagnosing stress incontinence. Abnormal mobility of the vesico-urethral segment should not mean that a patient has stress incontinence, nor does lack of abnormal vesico-urethral mobility mean that a patient should be continent.

Summary

Lateral cystograms done with a urethral catheter in place clearly define the vesico-urethral segment. Lateral X-ray films at rest and with straining while the patient is lying on the flat X-ray table determine the initial resting position and the degree of mobility of the vesico-urethral segment.

Normally the vesico-urethral junction is opposite the lower third of the pubic bone and moves about 0·5 to 1·5 cm downward and posteriorly with straining.

In true stress incontinence, the intrinsic urinary sphincteric mechanism is usually intact (unless surgically damaged), yet weakened by lack of pelvic support—which leads to excessive mobility and/or abnormal resting position of the vesico-urethral segment. Surgery can correct only these 2 defects if present.

Simplified cystographic studies can offer valuable information in confirming the diagnosis and in assessing the prognosis.

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Evaluation of Immunological Reactivity in Bladder Cancer

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The most suitable treatment of early invasive bladder cancer is still a matter of debate and the overall results of therapy are disappointing (Williams and Smith, 1973). Whilst it is appreciated that some patients do respond to local forms of therapy, others require cystectomy to control the disease and the decision and timing of major surgical intervention is frequently difficult. At present, it is not possible to predict how an individual will respond to a particular form of treatment. The variety of response to therapy strongly suggests that the host-tumour relationship plays a major role in the evolution of the disease and attempts have been made to find factors which have prognostic significance, and will assist in the selection of that form of therapy appropriate to the individual case (Cooper *et al.*, 1973).

In recent years it has been demonstrated that human bladder tumours possess tumour-specific antigens and that these antigens are common factors in a large proportion of bladder tumours (Bubenik *et al.*, 1970*a* and *b*). A similar phenomenon has been recognised in a variety of other human tumours, including neuroblastoma, adenocarcinoma of the colon, melanoma and osteosarcoma (Hellstrom *et al.*, 1971; Morton, Eilber and Malingren, 1971). Peripheral blood lymphocytes from patients who have bladder tumours exhibit cytotoxic effects when tested *in vitro* against bladder tumour cells maintained in tissue culture. This effect is seen whether the lymphocytes and bladder tumour cells are derived from the same subject or from different individuals (Bubenik *et al.*, 1970*a*). The studies of O'Toole *et al.* (1972) indicate that the cytotoxic response may change during the course of therapy and may be of prognostic value. However, the microcytotoxicity test in current use is time-consuming and seems unsuitable for general clinical application. This paper describes the exploration of an alternative method of measuring the patient's cytotoxic response against bladder tumour cells *in vitro*. The cytotoxic response in relation to clinical staging and pathological grading of bladder tumours has also been investigated.

Material and Methods

Patients

The study was performed on 69 male patients attending the Department of Urology at Leeds for investigation and treatment of bladder cancer and included primary and recurrent tumours. The length of history varied from a few months to more than 10 years. Histological confirmation of the disease was obtained by transurethral deep biopsy in every case. The specimens were classified according to the degree of cellular differentiation and invasion (Levi *et al.*, 1969) and the U.I.C.C. system for the clinical staging of bladder tumours was followed. Extent of invasion of the tumour was estimated from cystoscopic and bimanual examination under general anaesthetic. Patients with debilitating disease other than tumour, or who were known to have other forms of cancer, were excluded from this series, as were patients with significant urinary tract infection, a total white cell count in excess of 12,000/c.mm or a blood urea in excess of 45 mg/100 ml. The control group for the series comprised male patients attending the urological department or in-patients with urinary tract disease other than bladder cancer and fulfilling the general criteria for admission. They were age-matched with the bladder cancer patients.

Preparation of Blood Samples

30 ml of blood was obtained from unanaesthetised patients, 20 ml was defibrinated and approximately 8 ml was allowed to clot at 27°C to provide serum. Lymphocytes were separated from the defibrinated blood by a modification of the technique of Coulson and Chalmers (1964). Freshly prepared gelatine solution, 3% weight for volume in normal saline was added to the defibrinated blood and thoroughly mixed. The mixture was allowed to stand for 45 minutes at 37°C. The supernatant was then carefully removed and incubated for a further 30 minutes on a polystyrene column to remove the polymorphonuclear leucocyte fraction. The mixture was then eluted and found to contain between 90% and 96% pure mononuclear cells.

Target Cells

The T24 cell line of human bladder cancer cells maintained in tissue culture and supplied by the Wenner-Gren Institute, Stockholm, was used as the target (Bubenik *et al.*, 1973). This line had been derived 18 months previously from a moderately well differentiated papillary carcinoma of bladder, and demonstrated to contain tumour specific antigen (Bubenik *et al.*, 1973). The cells were maintained in glass or plastic flasks and passaged by trypsinisation. Waymouth's MB521 medium was used, supplemented with 10% foetal calf serum, 0·3 mg/ml of freshly prepared glutamine, penicillin 100 i.u. and streptomycin 100 mcg/ml. In some of the experiments, human kidney fibroblasts or HeLa cells were used as control targets.

The Cytotoxic Assay

A modification of the radioactive chromium release assay system was used to measure the cytotoxic activity of the lymphocytes. This is based on the principle that following damage to a cell, the permeability of the cell membrane is altered and permits the release of intracellular isotope. T24 cells were trypsinised, suspended in normal saline at 27°C and their concentration adjusted to 3×10^6 cell/ml. 100 microcuries of ^{51}Cr chromate (Radiochemical Centre, Amersham, England) per ml of cell suspension was added and the mixture incubated at 37° for 45 minutes with occasional gentle shaking. The tumour cells were then washed 3 times to remove the excess of ^{51}Cr chromate and the cells diluted to give a final concentration of 2×10^4 cell/ml in Waymouth's medium. Several factors influencing the release of ^{51}Cr chromate from the target cells were investigated as shown in the experimental protocol (Table I). Duplicate tubes were set up for each experiment and were incubated in a 5% CO_2 atmosphere for 18 hours. Each tube was then centrifuged at 3,000 r.p.m. for 5 minutes, 1 ml. of the clear supernatant carefully removed and the radioactive chromium content estimated in a well-type gamma counter. The released chromium was expressed as a percentage of the initial total chromium incorporation as shown in the formula:

$$\begin{array}{l}\text{Units of}\\ \text{Tumour}\\ \text{Specific}\\ \text{Cytotoxicity}\end{array} = \left(\frac{^{51}\text{Cr released (TEST)}}{^{51}\text{Cr total}\quad\text{(TEST)}} - \frac{^{51}\text{Cr released (CONTROL)}}{^{51}\text{Cr total}\quad\text{(CONTROL)}}\right) \times 100$$

and units of tumour-specific cytotoxicity derived for each test patient. The spontaneous release of chromium was high for this particular cell line.

Results

The objective of these experiments was to form a quantitative estimate for comparative purposes of the cytotoxic activity of lymphocytes and serum from bladder tumour patients. This would

Table I

Constituents of the Test System

Test System	1 ^{51}Cr labelled T24 Cells	2 Foetal Bovine Serum	3 Control Lymphocytes	4 Control Serum	5 Test Lymphocytes	6 Test Serum
Spontaneous release	+	+	−	−	−	−
Lymphocyte (control)	+	+	+	−	−	−
Lymphocyte (test)	+	+	−	−	+	−
Serum (control)	+	−	−	+	−	−
Serum (test)	+	−	−	−	+	−
Lymphocyte + serum (control)	+	−	+	+	−	−
Lymphocyte + serum (test)	+	−	−	−	+	+

1. ^{51}Cr Labelled T24 Cells	2×10^4 in 1 ml
2. Foetal Bovine Serum	0·3 ml.
3. Control Lymphocytes	2×10^6 in 1 ml.
4. Control Serum	0·3 ml.
5. Test Lymphocytes	2×10^6 in 1 ml.
6. Test Serum	0·3 ml.

All tubes made up to exactly 3 ml with MB752/1 medium

Table II

Experimental Example—Effect of Lymphocytes and Serum on Release of ^{51}Cr Chromate, from T24 Bladder Tumour Cells

	Lymphocytes		Serum		Lymphocytes and Serum	
Patient	% ^{51}Cr Release	Cytotoxic Units	% ^{51}Cr Release	Cytotoxic Units	% ^{51}Cr Release	Cytotoxic Units
Control	55	4	50	0	54	3
Test T3 tumour	64	13	55	4	59	8
Test T1 tumour	74	23	54	3	68	17
Cell control	51	...	...	...	...	...

T1 and T3 refer to tumour stage.

allow a direct comparison between different patients, and assessment of the the effects of therapy by monitoring the cytotoxic response in the individual patient on repeated occasions. This was found to be impractical since the general range of cytotoxicity was small, and on repeated testing of the same patient and the same control, the variability factors were too great to allow direct comparisons to be made. However, repeated testing of bladder tumour patients showed consistent cytotoxic activity in most samples, and patients who produced a cytotoxic response could be distinguished from those who did not. The highest values of cytotoxicity were obtained in patients with well differentiated, non-invasive lesions and those with multiple papillary tumours. A typical experiment is shown in Table II.

When considered in relation to clinical staging, a progressive decrease in both peripheral blood cell cytotoxicity and of serum cytotoxicity was observed as the disease progressed (Table III). This was most noticeable in T1 lesions of whom the majority showed both cellular and serum cytotoxicity, and in T4 lesions in whom no cytotoxic activity was found. T2 and T3 tumours gave comparable values which may reflect the clinical difficulty of distinguishing between these lesions. When lymphocytes and serum from the same patient were added to the target cells, the serum was found to contain a reduction factor which decreased or abolished the cytotoxic effect produced by the lymphocytes alone. This was found in almost all cases with invasive tumour (Tables III and IV).

Table III

Incidence of Lymphocyte Cytoxicity, Serum Cytotoxicity and Lymphocyte Cytoxicity Reduction Factor in Human bladder Tumour Patients/Clinical Staging

Tumour Stage	No.	Lymphocyte Cytotoxicity		Serum Cytotoxicity		Reduction Factor Present	
		No.	%	No.	%	No.	%
T1	37	26	(70)	23	(68)	8	(31)
T2	17	8	(47)	5	(34)	7	(87)
T3	12	5	(42)	3	(30)	5	(100)
T4	3	0	(0)	0	(0)	0	...

Table IV

Incidence of Lymphocyte Cytotoxicity, Serum Cytotoxicity and Lymphocyte Cytotoxicity Reduction Factor in Human Bladder Tumour Patients/Pathological Grading

Tumour Path. Grade	No.	Lymphocyte Cytotoxicity		Serum Cytotoxicity		Reduction Factor Present	
		No.	%	No.	%	No.	%
Well differentiated non-invasive	28	22	(76)	18	(62)	11	(50)
Well differentiated invasive	4	0	(0)	2	(50)	0	...
Poorly differentiated invasive	16	4	(25)	8	(50)	4	(100)
Anaplastic	3	2	(67)	3	(100)	2	(100)

Pathological grading showed a similar picture, non-invasive lesions showing 76% cytotoxicity in the presence of active disease (Table IV). This was markedly reduced with dedifferentiation of cellular structure and invasion. However, the truly anaplastic tumours seemed to form a class of their own. All 3 patients tested in this group showed serum cytotoxicity and only 1 failed to show cellular activity. The addition of serum, however, totally abolished the lymphocyte cytotoxic effect in both cases examined.

Discussion

The lack of consistency on repeated testing remains a major problem in cytotoxicity experiments and is due to many variables. The target cells derived from the cell line may be weakened at the time of testing by nutritional difficulties, sub-liminal infection, mechanical damage due to handling, and may contain varying proportions of particularly vulnerable cells which are not detected by the dye-exclusion methods. The use of synchronised cell lines may be of assistance in resolving this problem. The peripheral blood samples may also show considerable variability, and this is not directly related to the peripheral white cell count. It may be due to the chance selection of varying proportions of sensitised lymphocytes and at the present time there is no simple technique to identify these cells in advance in human patients. The separation of lymphocytes from peripheral blood remains technically laborious and requires impeccable technique to obtain satisfactory preparations. The method used here has the advantages of economy and simplicity from the point of view of laboratory equipment, particularly when large numbers of blood samples are handled. Chromium labelling is a simple technique but is frequently not suitable for use with human tumour lines. Spontaneous release remained consistently high throughout these experiments and could not be reduced below 45% despite repeated washing, careful cell handling and variation of the incubation schedules.

One serious objection, however, is the control situation. Lack of consistency in non-specific chromium release precludes the use of this method for comparative purposes in different experiments. Nevertheless, it does seem possible to differentiate between those patients who have cytotoxic peripheral blood cells and serum, and those who have not, and this allows several general points to be made. In relation to clinical staging, a negative correlation was demonstrated with the degree of invasion of the tumour both on lymphocyte and serum testing. In some cases, the sera or lymphocytes had an independent cytotoxic action which was reduced when the two were combined. This was most noticeable when the tumour became invasive, only 1 patient out of 13 tested failing to show this property although 8 of the 13 still retained the capacity to produce cytotoxic effects on tumour cells when the serum factor was tested alone. The presence of this cytotoxicity reduction factor in the serum of patients with advanced disease may be analogous to the blocking factor described by the Hellströms (Hellström *et al.*, 1971) in both animals and human patients. When found in patients with apparently localised lesions, this factor may indicate that the cancer is more aggressive than suggested by clinical or histological examination, and that more extensive surgery is required at this stage to adequately control the disease. These experiments have also emphasised the importance of the influence of serum factors on cell-mediated immunity. The formation of a population of cytotoxic lymphocytes, sensitised specifically against tumour cell antigens, appears fundamental to the control of tumour development. Possibly, however, the serum factors ultimately determine the outcome in the individual patient. Further analysis of these factors seems imperative before the considerable potential of immunotherapy can be used scientifically in the clinical situation. At present, the results obtained here are of considerable interest but require further technical development and controlled immunological investigation before their significance can be properly evaluated. It does seem clear, however, that the presence of a bladder tumour produces an immune response in the host which is readily detectable by *in vitro* testing and that this response is lost in aggressive and advanced disease. It will be of considerable interest to observe with the passage of time whether those patients with localised disease who do not have a detectable cytotoxic response, or who have the reduction factor present in their sera, have ultimately a poor prognosis.

Theoretically using a tissue culture line in these experiments might be considered to be a source of confusion as it would be impossible to tell if the cytotoxicity is directed against the transplantation antigens or tumour specific antigens. In practice Bubenik *et al.* (1973) found that in studies of T24 in the microcytotoxicity test system over a period of 30 months that leucocytes from various sources exhibited cytotoxic action against this line as follows: 25/43 from patients with bladder cancer, 2/40 from patients with unrelated tumours and 0/13 from patients without tumours. We used the T24 line to see if reacting the patients' cells against a common antigen could be the basis of a rapid quantitative measurement of the cellular immunity against bladder tumour antigens. However, for the various reasons stated above, our approach does not seem to be sufficiently precise although the general pattern of response corresponds with previous results.

Summary

The cytotoxic activity of lymphocytes from patients with bladder cancer on T24 bladder cancer cells in tissue culture have been studied. The technical problems are described and the suitability of the method as part of the assessment of the patients' immune reactivity discussed. On balance the technical difficulties outweigh its theoretical advantages.

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The Control of Severe Bleeding from the Bladder by Intravesical Hyperbaric Therapy

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Sustained high intravesical pressure has been advocated as a treatment of carcinoma of the bladder (Helmstein, 1972) and a similar technique has been used to control severe haemorrhage secondary to a variety of pathological changes in the bladder wall (Holstein *et al.*, 1973). As part of our present investigation of intravesical hyperbaric therapy, 8 patients have undergone a total of 9 treatments for severe prolonged haemorrhage due to radiotherapy changes, bladder tumours or both. In each case conservative therapy had failed. The results have been encouraging and are presented here.

Method

Details of the patients treated are summarised in Table I. In each case bleeding was severe and recurrent, necessitating hospital admission, and blood transfusion of up to 6 units of blood. The bladder contained varying amounts of clot, producing retention in some. Conservative management including evacuation of clot, catheterisation, blood transfusion and administration of epsilon aminocaproic acid produced no lasting effect.

Table I

Patient	Sex	Age	Duration of Bleeding	Aetiology
J. P.	M	72	4 months	Radiotherapy
M. C.	F	50	7 weeks	Radiotherapy
A. A.	M	85	2 years	Multiple non-invasive tumours
F. F.	M	70	2 months	Multiple non-invasive tumours
P. A.	M	74	7 weeks	Radiotherapy and recurrent invasive tumour
L. H.	F	77	3 weeks	Radiotherapy and recurrent invasive tumour
H. O.	M	73	3 weeks	Radiotherapy and recurrent invasive tumour
W. B. (1)	M	57	4 months	Radiotherapy and recurrent invasive tumour
W. B. (2)	M	57	1 month	Radiotherapy and recurrent invasive tumour

Intravesical hyperbaric therapy was performed by inflating a balloon within the bladder, the apparatus being made in the manner described by Helmstein and summarised here. The tip of a round-ended 18 F. latex Foley catheter was cut off and placed within an ordinary rubber party-type balloon. The balloon was tied to the distal part of the catheter so that the Foley balloon could be inflated inside it (Figs. 1 and 2). After assembly the apparatus was sterilised by immersion in 1 : 2,000 aqueous chlorhexidine solution for 30 minutes and was discarded after being used once.

Regional epidural anaesthesia using epidural bupivacaine 0·5% was used in all cases. It was administered through an epidural catheter introduced between the 4th and 5th lumbar vertebrae.

With the patient in the lithotomy position, the balloon, stretched out on a curved catheter introducer, was introduced into the bladder along the urethra. This technique has been found easier than passing the apparatus through a resectoscope sheath as advocated by Helmstein. The loose catheter tip was used to cover the end of the introducer and so prevent perforation of the balloon. Once introduced, the Foley balloon was inflated with sterile water and pulled back until it was felt to impinge on the bladder neck, thus confirming that the main balloon was within the bladder. The patient was then placed in the supine position and the balloon slowly inflated with sterile saline from a central venous pressure monitoring set. The balloon pressure, measured relative to the pubic symphysis, could thus be monitored throughout treatment. In each case the final pressure was adjusted to exceed the patient's diastolic blood pressure by 25 cm water as preliminary studies had shown that approximately this amount of pressure was lost in overcoming the elasticity of the balloons used. We have measured the pressure-volume characteristics of each balloon when exposed to atmospheric pressure and it has been found that the pressure loss due to elasticity may vary to some extent from one balloon to another. It is advisable therefore to check the basic pressure values before use. In the present series the final pressure was usually between 115 cm and 145 cm water pressure and this was rarely exceeded in order to minimise the risk of bladder perforation (Helmstein, 1972). After 6 hours at maximum pressure the balloon was removed and the patient catheterised with a 20 F. Foley catheter. Closed drainage was maintained for 4 days or longer, until the urine was clear of blood. Urine output was measured daily, urine culture and blood urea twice weekly.

Table II

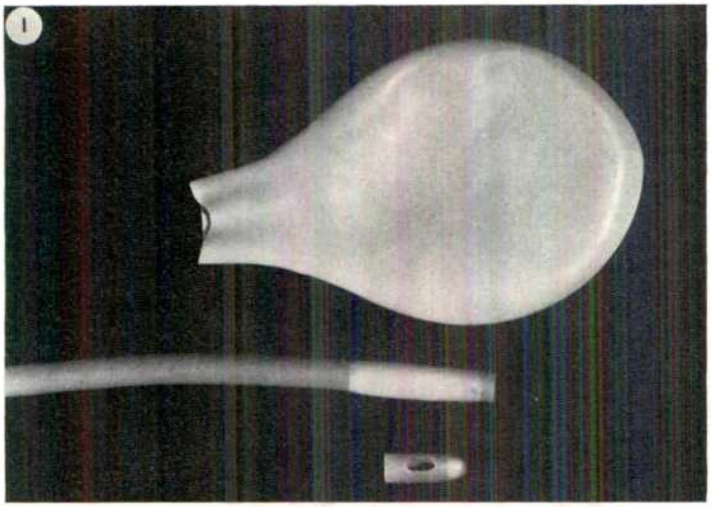
Patient	Duration of Post-treatment Bleeding	Recurrent Bleeding	Follow-up Period (months)	Progress
J. P.	24 hours	None	4	Routine tumour follow-up
M. C.	24 hours	Slight after 2 months	7	Out-patient follow-up
A. A.	3 days	After 2 weeks	4	Refused further treatment
F. F.	2 days	None	6	Retreated (recurrent tumour)
P. A.	13 days	Moderate after 2 months	4	Recurrent tumour resected (bleeding stopped)
L. H.	24 hours	None	6	Died (inoperable tumour)
H. O.	24 hours	None	3	Retreated (recurrent tumour)
W. B. (1)	24 hours	Intermittent after 1 month	2	Retreated (W.B.2)
W. B. (2)	24 hours	None	2	Routine tumour follow-up

Results

The results of treatment are summarised in Table II. Six patients were bleeding from a previously irradiated bladder. The remaining 2 patients were bleeding from extensive, non-invasive bladder tumours and had not received radiotherapy. One of these failed to respond to hyperbaric therapy and refused any further treatment. Therapy was considered to have been successful when bleeding stopped within a few days, and further treatment was not necessary. A successful result was achieved in 8 out of 9 treatments and although the follow-up period is short (2 to 7 months), severe bleeding has recurred in only 2 patients. In 1 of these, bleeding ceased after transurethral resection of recurrent tumour, and in the other, bleeding stopped after further hyperbaric therapy.

There was no mortality related to the therapy and morbidity was slight. During distension of the bladder, 2 patients felt cold and shivered. Blood cultures taken at this time remained sterile but broad spectrum antibiotics were administered as a precaution. The phenomenon was short-lived and therapy was safely continued. Nausea and vomiting were common during the early stages of therapy. Anti-emetic agents were given early to prevent sudden swings in intra-abdominal pressure which may predispose to rupture of the bladder (Helmstein, 1972). Three patients had temporary urinary incontinence which disappeared after a few days without further treatment.

All patients maintained a good urine output. Postoperative diuretics were not used and renal function remained unchanged in all cases.



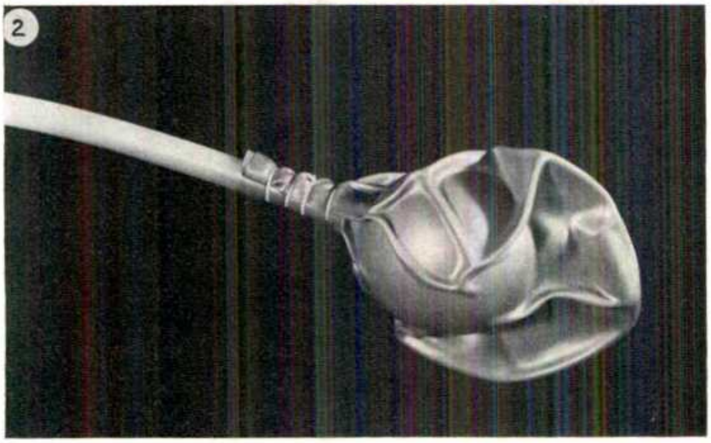


Fig. 1. The catheter and balloon before assembly.

Fig. 2. The assembled apparatus with the Foley balloon inflated.

Discussion

Severe haemorrhage from the bladder, particularly after radiotherapy, may be difficult to control. Conservative methods of treatment have been well summarised elsewhere (Turner, 1961; Goldstein, d'Escrivan and Allen, 1968) but they frequently fail to stop the bleeding. Cryosurgery has proved to be successful in a small number of cases (Cahan *et al.*, 1970), but its effect on the bladder and surrounding tissues cannot be predicted (Gibbons, 1966). Surgical intervention by open excision and diathermy of bleeding areas (Turner, 1961) or ligation of the internal iliac arteries (Goldstein *et al.*, 1968) may be successful, and should all else fail, cystectomy may be necessary.

In a recent series, hyperbaric therapy using intravesical pressures in excess of the patient's systolic blood pressure, has been used to control haemorrhage from the bladder in 6 cases (Holstein *et al.*, 1973). Our results confirm these findings but in our experience maximum pressures only just in excess of the patient's diastolic blood pressure have been equally effective, and there is less risk of tearing the bladder (Helmstein, 1972). This effective, relatively simple treatment can be performed on poor risk patients and has a reasonably long-lasting effect with few side-effects. Moreover it can be safely repeated. The results indicate that it can be used to advantage in cases of severe haemorrhage from the bladder wall where conservative methods have failed and before major surgical procedures are attempted.

Summary

Intravesical hyperbaric therapy has been used successfully to control severe haemorrhage from the bladder following radiotherapy and multiple tumours in 8 treatments on 7 patients.

A good long-term palliative effect has also been achieved in the majority.

The treatment is relatively free from side-effects, can be repeated, and is recommended as the primary treatment in bleeding from the irradiated bladder free of tumour and in the otherwise inoperable patient.

In operable lesions it controls the bleeding long enough for the patient to be adequately prepared for major surgery.

We would like to acknowledge the considerable help given to us by the Anaesthetic Department and the devoted attention of the Sister and Nurses on the Keeling Ward. We are indebted to the Photographic Department of the United Sheffield Hospitals for the photographs.

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A Personal Experience with 37 Turner-Warwick Scrotal Inlay Urethroplasties

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Scrotal inlay urethroplasties are now established as a good definitive alternative to frequent and difficult dilatations of urethral strictures, regardless of their aetiology.

A number of successful scrotal inlay urethroplasties have been described including Johanson (1953) with an anterior based scrotal funnel, Turner-Warwick (1960, 1968) using a wide posteriorly based funnel inlay, Gil Vernet (1966) with a lateral scrotal inlay and Blandy, Singh and Tresidder (1968) using a much exaggerated method developed by Leadbetter (1960) where the flap is constructed from vascular elastic scrotal skin rather than the inelastic skin of the perineum.

It is an advantage to use a technique which is flexible, allowing repair of strictures in the region of the membranous urethra, which can also be extended distally for the repair of the whole urethra from the verumontanum to the glans, even if perineal urinary fistulae are present as in 6 of these cases (Fig. 1).

A personal experience during a 4-year period with 37 Turner-Warwick urethroplasties is recorded, with particular emphasis on any problems that have been encountered, for there is little in the literature on the follow-up of such cases (Turner-Warwick and Ashken, 1970; Brendler and Jacobson, 1971).

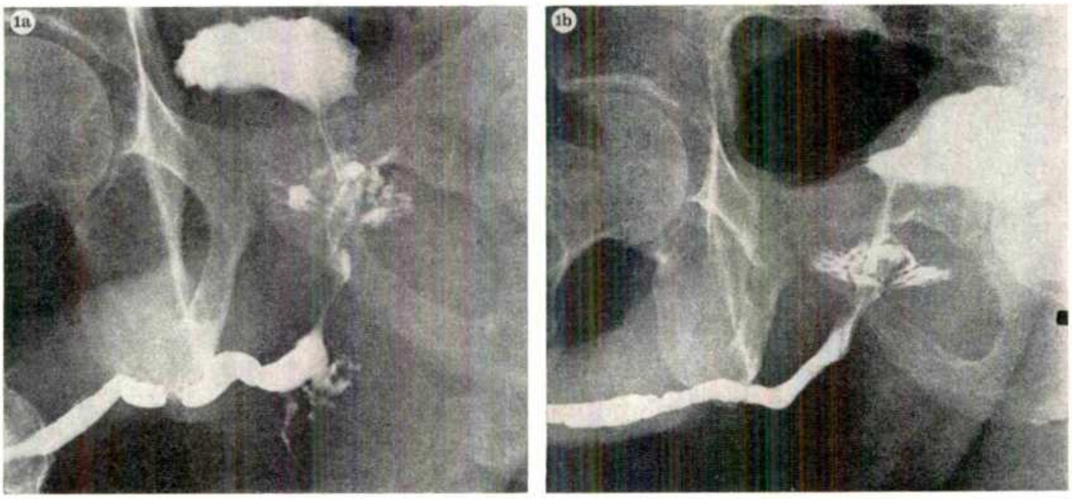


Fig. 1. Perineal fistula. (*a*) Post-gonococcal penile and membranous urethral stricture with perineal fistula from the bulbar urethra and evidence of old prostatitis. (*b*) A full-length urethral reconstruction was required. Urethrogram 3 months after closure shows a smooth urethra of normal calibre.

Table I

Aetiology of 37 Urethral Strictures

Congenital		3
Traumatic		13
Fall astride	7	
Fracture of pelvis	6	
Iatrogenic		4
Cystoscopy in childhood	1	
T.U.R.	2	
Hypospadias repair	1	
Post-infective		9
Gonococcal urethritis	6	
Non specific urethritis	3	
Unknown		8
		37

Table II

Length of History of Stricture

Under 1 year	6
1-5 years	4
6-10 years	2
11-15 years	5
16-20 years	5
Over 20 years	15

Aetiology of Stricture

This is probably unimportant in considering the indication for urethroplasty, but may influence the type of urethroplasty performed. Rather than attempting a staged scrotal inlay urethroplasty through the dense scar tissue of a supra-membranous urethral stricture following an unstable fracture of the pelvis, it might be preferable to use a 1-stage urethroplasty, with mobilisation of the penile and bulbar urethra to allow a direct anastomosis to the prostatic urethra (Turner-Warwick, 1973). This technique is less empirical than any pull-through urethroplasty (Badenoch, 1950; Wells, 1966) and has been used on 2 cases not included in this series.

Post-gonococcal urethritis and trauma to the urethra, from either a fall-astride injury or fractured pelvis, accounted for 19 of these strictures, but in 8 the aetiology remained unknown and in 3 others the age of onset of symptoms suggested a congenital stricture (Table I). There were no tuberculous or malignant strictures in the series. There were 3 submembranous and 3 supramembranous strictures, the remaining 31 cases having posterior bulbar strictures, with the soft tissue damage usually being much more extensive than demonstrated on the urethrogram and hence requiring a trans-sphincteric scrotal inlay.

Length of History of Strictures and Dilatation

In 25 of these patients, regular, frequent dilatations had been done for over 10 years, whilst post-traumatic strictures accounted for the 6 cases having urethroplasties within 1 year (Table II).

Whilst the majority of men with urethral strictures are still treated by regular dilatation (Devereux and Burfield, 1970), review of such cases emphasises that they should all have had a urethrogram, (Turner-Warwick and Worth, 1970). Not only will this demonstrate complicating false passages, fistulae or urethral stones, but it will confirm whether or not a true urethral stricture exists, for it is likely that many men without genuine urethral strictures have unnecessarily become members of a "dilatation clinic", from which it is difficult to escape.

A micturating cystourethrogram may give more information about the degree of functional obstruction caused by a urethral stricture compared with an ascending urethrogram (Fig. 3).

Technique of Urethroplasty

Basically this has been as described by Turner-Warwick (1968), with use of the armamentarium of special urethroplasty instruments (Fig. 4).

For the first 10 cases, either monofilament nylon or chromic catgut sutures were used, but since July 1970, 3 × 0 or 4 × 0 Dexon sutures have been used for all stages of these urethroplasties.

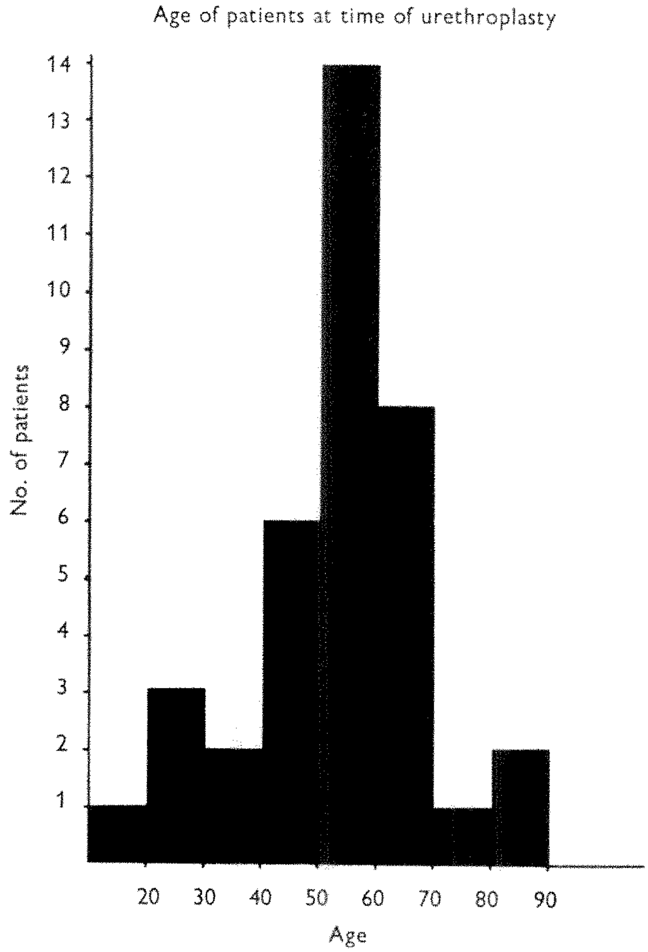


Fig. 2. Age of patients at time of urethroplasty.

Age Distribution at Time of Urethroplasty

The majority of these patients were between 40 and 70 years of age, the youngest being 15 years and the oldest 84 years (Fig. 2). Old age was not considered a contra-indication to urethroplasty, for not only are the elderly just as delighted as younger men to be released from a life revolving around their next urethral dilatation, but 4 such patients have elected to remain with the first stage of their urethroplasty, content to pass urine with a good stream and full control, involving no greater inconvenience than having to sit to void, as practised by the majority of the normal population.

In this series, the introduction of Dexon absorbable sutures is considered to be a major contribution to the technique of scrotal inlay urethroplasty. This has avoided the tissue reaction seen around catgut sutures and the difficult removal of non-absorbable sutures, which requires a general anaesthetic and may well cause some tissue damage in the depths of the scrotal inlay suture line. Healing with Dexon has been good and there have been neither soggy nor infected wounds as a complication of Dexon as described by some urological surgeons.

Progress of 37 Urethroplasties

Twenty-five of the 37 cases have had their urethroplasties closed, 12 of these within 6 months of their first stage operation (Fig. 5). Four urethroplasties have been closed for over 3 years and 9 closed for over 2 years. The minimum period between the first stage and the closure was 4 months, to allow the scrotal inlay to become stable with a good blood supply and no tendency to restenosis.

Interval Review

Following the scrotal inlay these cases were reviewed monthly as out-patients, to calibrate, but not dilate, the urethrostomy ostia and to separate any superficial bridging across the opened urethra. A 26F sound should pass without difficulty. After 3 months, the urethroplasty was reviewed under a general anaesthetic combined with both depilation of the inlaid scrotal skin using a fine needle attached to a 12-volt D.C. current, and a cystoscopy, to inspect the bladder and prostate. In 1 case, an advanced invasive carcinoma of the bladder was found unexpectedly and necessitated a total cystectomy and urinary diversion instead of closure of the urethroplasty. The importance of the interval review cannot be overemphasised, for this period must not be compromised by impatience of either the patient or the surgeon.

Eighteen of the 25 cases closed required no readjustments of the scrotal inlay, whilst 3 cases required up to 6 advancements of the scrotal skin before it became stable, with no splitting on calibration of the urethrostomy openings. Readjustments may follow an error in technique, in not getting the initial posterior sutures high enough through the area of the intrinsic urethral sphincter. The ability to be able to review and adjust, particularly the funnelled posterior urethrostomy of these urethroplasties, with vascular elastic scrotal skin available for advancement into the posterior urethra is one of the advantages, rather than a criticism of this technique. In only 2

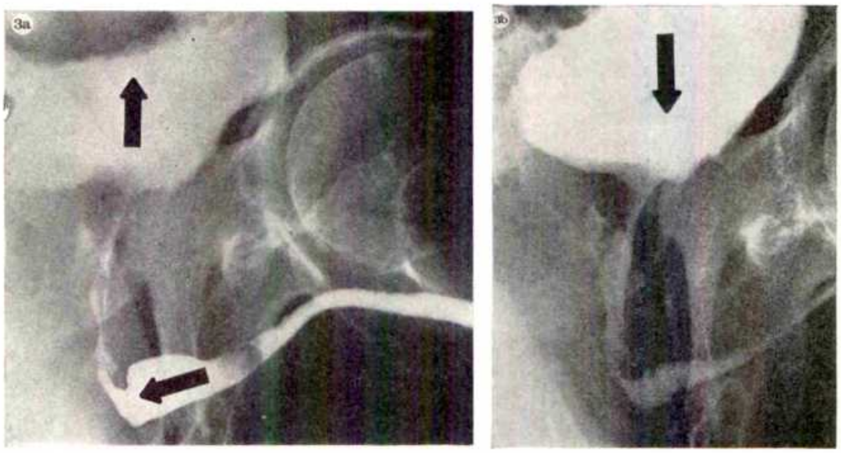
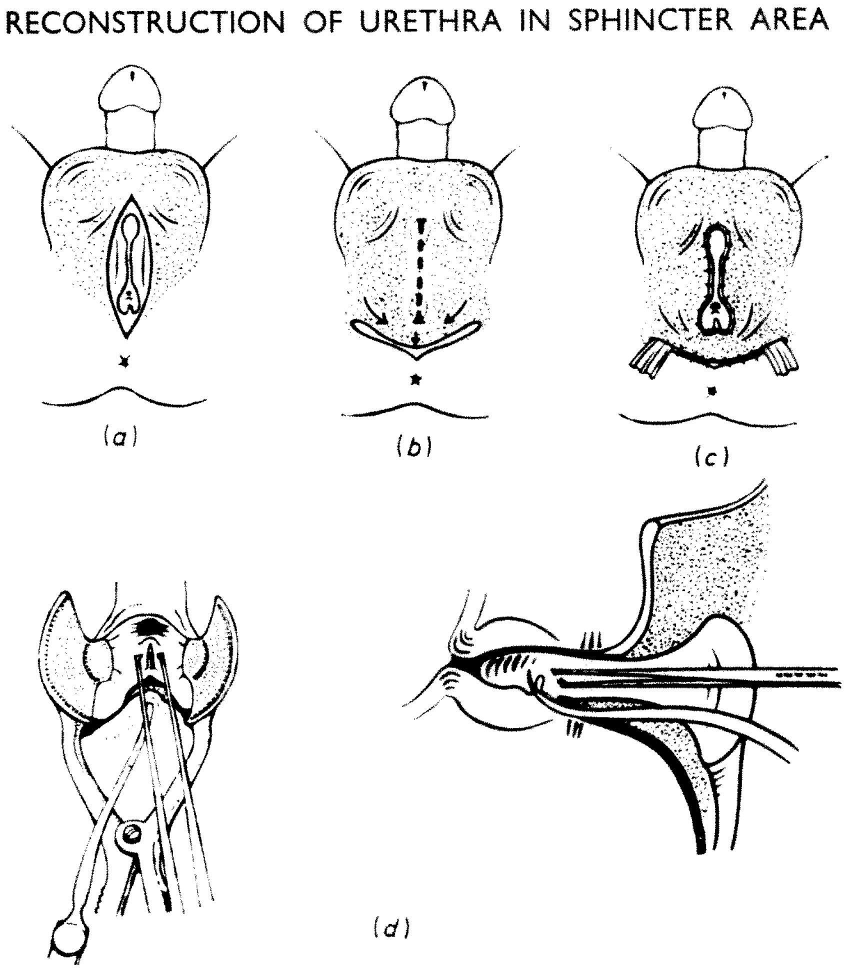


Fig. 3. Aged 60 years, having had urethral dilatations every 4 weeks for 29 years following a fractured pelvis and ruptured membranous urethra. (*a*) Ascending urethrogram showing a posterior urethral stricture, but this static investigation gives no information about the degree of functional obstruction caused by this stricture. (*b*) The voiding cystourethrogram confirms the posterior urethral stricture but there is free flow of the contrast through the stricture with no dilatation of the proximal urethra or evidence of functional bladder outflow obstruction. This patient was persuaded to stop having 4-weekly empirical dilatations and now has sounds passed easily every 6 months, so that urethroplasty has not been advised.

cases in this series was there a shortage of scrotal skin, both having had previous scrotal operations, but this did not prevent using a posterior based inlay.

The 7 cases in which difficulty has been experienced in obtaining a stable scrotal inlay had all been frequently dilated for between 14 and 26 years; failed Johanson urethroplasties had been previously performed in 2 cases and perineal urinary fistulae were present in 3 cases. There was no constant or common aetiology causing these intractable strictures. In spite of these technical problems, all these patients were delighted with their micturition, even after the first stage operation, compared with their urological plight prior to their urethroplasty. One patient was content with weekly self-dilatation of the posterior urethrostomy opening, allowing him to travel and lead a full life.



RECONSTRUCTION OF URETHRA IN SPHINCTER AREA

Fig. 4. Turner-Warwick scrotal inlay urethroplasty. (*a*) The structure and normal urethra proximal and distal to it are opened through a midline perineal incision extending from well on to the scrotal skin to just anterior to the anus. (*b*) The scrotal skin is mobilised with bunching of the vascular elastic subcutaneous tissue towards the cut edge of the scrotal skin which is then invaginated into the open urethra. (*c*) A secondary midline incision is made into the scrotum anterior to this scrotal bridge; its margins are sutured to the opened urethra producing a funnelled posterior urethrostomy opening with mobile, vascular, elastic skin available for later readjustments if necessary. (*d*) The posterior apex of the secondary scrotal incision is inlaid and sutured just below the verumontanum with the aid of the special posterior urethral needle and fibre-light posterior urethral speculum.

Four of the cases closed, and 4 others awaiting closure, have had *scrotal skin rotated* on to the penis to give enough skin for a complete tube closure of the new urethra, in preference to using a buried strip of skin technique (Browne, 1949).

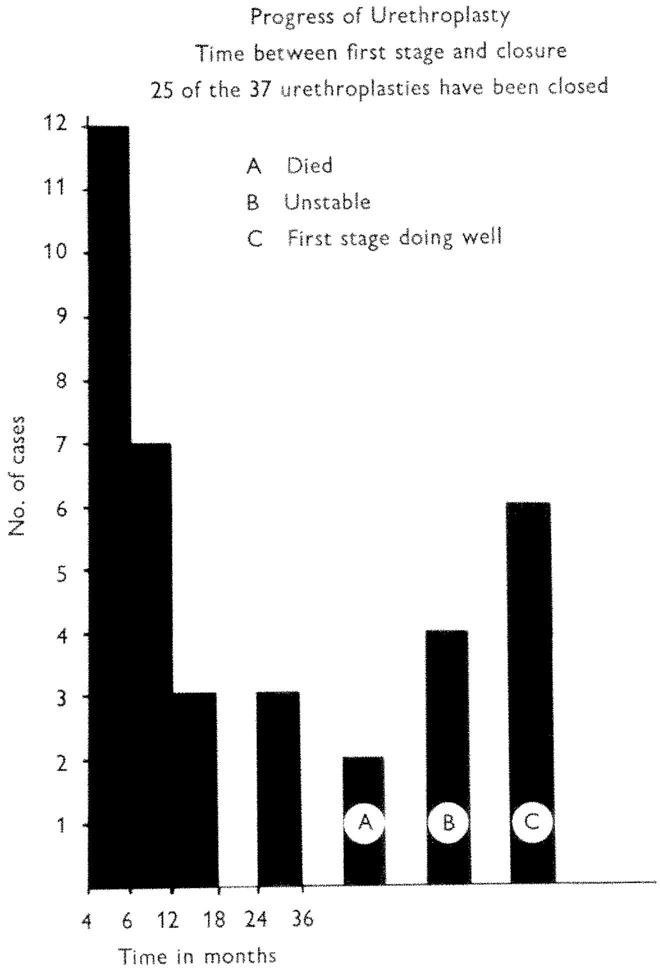


Fig. 5. Progress of urethroplasty. A majority of the cases are closed with stable scrotal inlays requiring no readjustments. Four cases are being troublesome with unstable scrotal inlays requiring several readjustments. They have all had either Johanson urethroplasties previously or severe perineal scarring with fistulae or difficult dilatations for over 20 years. Two cases have died with good stable scrotal inlays, 1 from an invasive bladder carcinoma and 1 from a strangulated bowel obstruction with peritonitis.

Closure and Drainage

In 4 cases closed, a "pull-in" suprapubic catheter was inserted for about 10 days. A small suprapubic incision is made on to the palpable tip of a urethral sound introduced into the distended bladder. After separation of the recti the bladder wall is identified and incised. The sound has a hole bored close to its tip so that a nylon sling can be loop-knotted after passing through the catheter which is then guided into the bladder on withdrawing the urethral sound. In the last 21 cases, the tubed urethra has been closed, over two 12 French gauge urethral catheters, using short runs of 4 × 0 Dexon, with removal of one of these catheters at the end of the repair. Many of these patients had scarred suprapubic areas from previous trauma or operations, which, combined with a common increase in weight following their scrotal inlay, made suprapubic catheterisation difficult. A urethrogram has been done 3 to 4 months after closure of the urethroplasty. Bouginage has been avoided.

Table III

Complications

Early	Slough	1
	Epididymo-orchitis	2
	Fistula	1
Intermediate	Granulation tissue	5
	Incontinence	2
	False passage	1
	Readjustment	12
Late	Post-micturition dribble	6
	Impaired ejaculation	4
	Restenosis	1

Complications (Table III)

Sloughing. Loss of part of the deep scrotal inlay was seen only once with subsequent scar formation requiring later readjustment of the scrotal skin.

Acute Epididymo-orchitis. In spite of prophylactic antibiotics, 2 patients developed epididymo-orchitis within 4 weeks of their scrotal inlay which responded to more prolonged courses of antibiotics. *Urinary tract infection* was a recurrent problem in 2 cases after closure of their urethroplasty and has required long-term antibiotic therapy.

Urinary Fistulae. This occurred only once and was associated with a pyocyaneous urinary infection with a suprapubic catheter in place. The fistula healed spontaneously with a further 1 week's urinary diversion via the suprapubic catheter and no sequelae have developed.

Haemorrhage. This has not been a problem during the scrotal inlay operation, provided temporary stay sutures were inserted to control venous bleeding from the incised corpus spongiosum, followed by incorporation of this vascular tissue in the short runs of sutures giving urethro-cutaneous apposition.

An unexpected severe secondary urethral haemorrhage occurred in 1 case, 10 days after rupture of the bulbar urethra from a straddle injury, which had been treated with a suprapubic catheter and no instrumentation or catheterisation of the urethra. This haemorrhage required a 5-pint blood transfusion and emergency ligation of the internal iliac arteries. A scrotal inlay urethroplasty was done 6 weeks later and was closed after 9 months. Such cases may be better managed with an emergency urethrogram and one stage repair of the freshly injured urethra.

Bridging. Granulation tissue and flimsy adhesions may occur between the suture lines across the opened urethra or urethrostomy ostia. This has been less common since using Dexon sutures and the adhesions usually respond to gentle digital separation until the suture line is epithelialised.

Incontinence. The patients were usually completely continent after the scrotal inlay, even when the inlay had been taken through the urethral sphincter area in treating supramembranous and

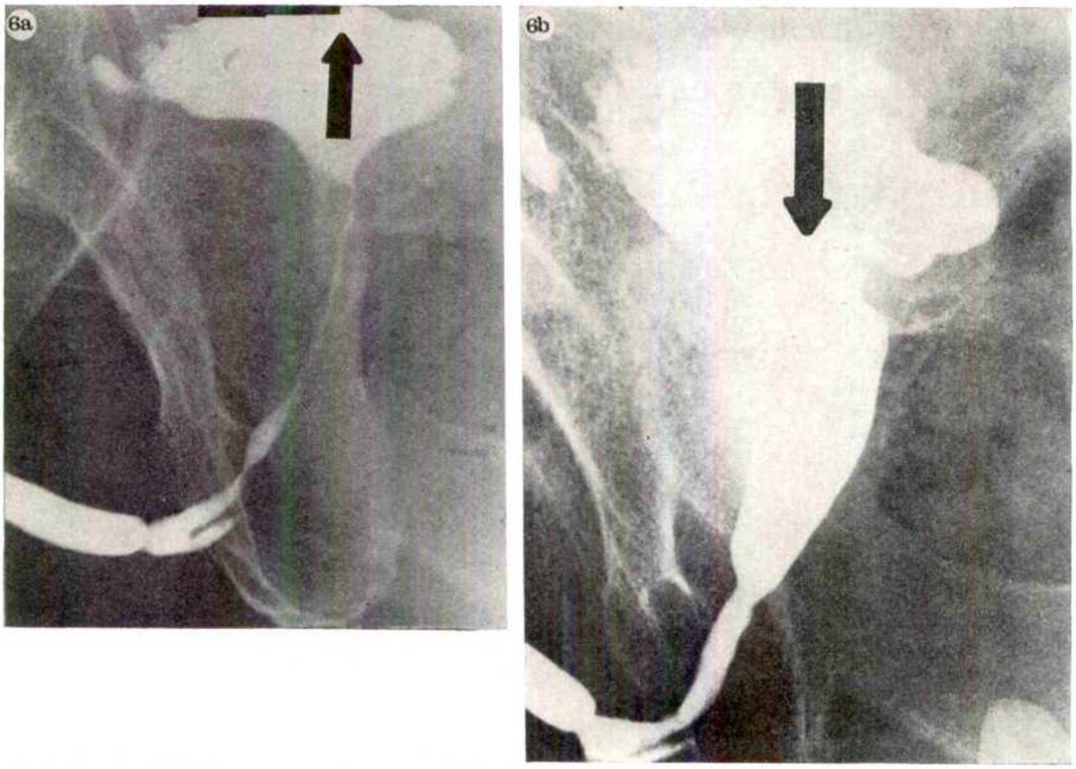


Fig. 6. Continence after a previous bladder neck resection. (*a*) Urethrogram showing distal penile and bulbar urethral strictures treated with dilatations every 2 months. The prostatic urethra is poorly filled due to hold up of the contrast by the strictures. (*b*) Micturating cystourethrogram gives more functional information, with dilated prostatic urethra proximal to stricture. The bladder neck is incompetent following the previous endoscopic resection. In such cases a transphincteric scrotal inlay may result in urinary incontinence.

posterior bulbar strictures. A transurethral resection of the bladder neck and prostate had been previously performed in 3 patients (Fig. 6); continence in such cases having had both a prostatectomy and urethroplasty may be due to the external sphincter taking up a new "passive" role in the absence of an internal sphincter and an intact intrinsic urethral musculature (Edwards *et al.*, 1972). Continence at rest depends on having an occlusive competent bladder neck sphincter supported by an intact urethral musculo-elastic mechanism. Using voiding cine cystourethrograms, Turner-Warwick (1968) has emphasised that after dilatation of the membranous urethra to finger-size followed by a scrotal inlay to the level of the verumontanum, the intrinsic urethral mechanism is occlusive at rest.

One patient was totally incontinent both before and after completion of his urethroplasty, probably due to damage to his sphincter mechanism from a combination of a fractured pelvis with ruptured posterior urethra and 20 years' frequent urethral dilatations, complicated by false passages (Fig. 7).

Balanitis xerotica with scarring and stenosis of the external urethral meatus resulted in an overflow urinary incontinence in 1 patient who developed a large wide-necked urethral diverticulum (Fig. 8).

Post-micturition Dribbling. This has been a slight inconvenience in 6 cases after closure of their urethroplasties and is due to some redundancy of the new tubed urethra, which may also lack compressive support from the reconstruction of rather fibrous bulbar muscles.

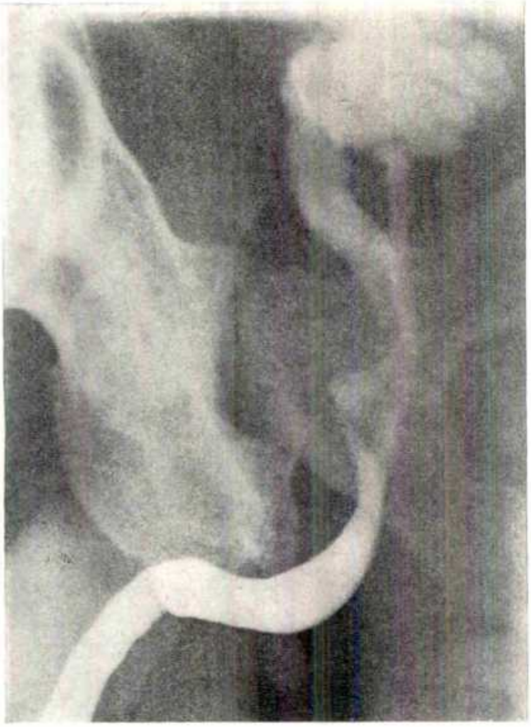


Fig. 7. False passages. Posterior urethral false passage connecting with the bladder resulting from regular dilatations for 23 years of a membranous stricture following a fractured pelvis. Urinary incontinence for 6 months prior to scrotal inlay urethroplasty. It is advisable to open the bladder at the time of the first-stage urethroplasty to ensure that the scrotal inlay is sutured to the true urethra and not along a false passage. Incontinence persisted after the urethroplasty probably due to previous sphincter damage. Also impotent after urethroplasty having had normal erections but no ejaculation following his pelvic injury.

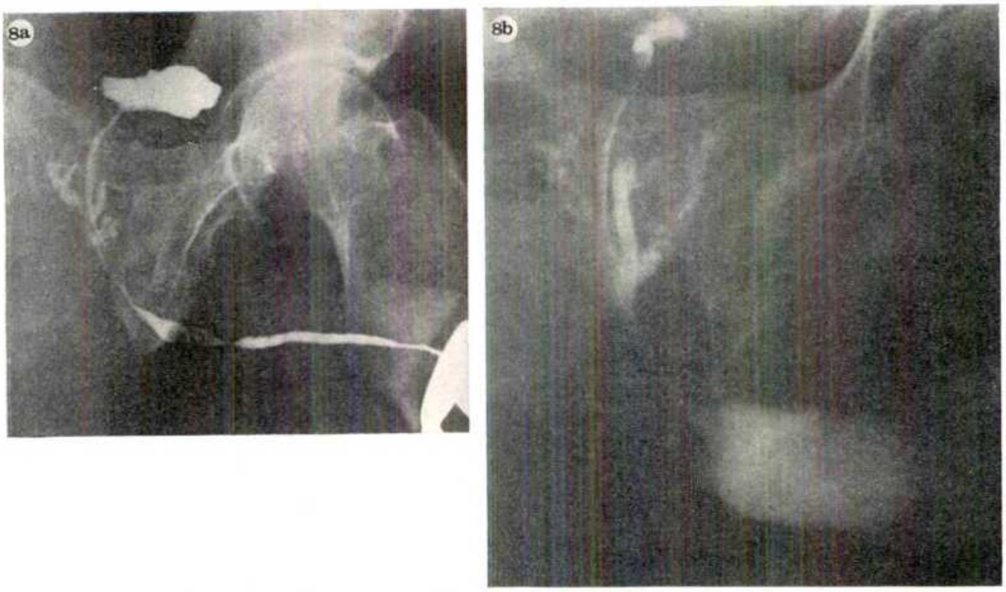


Fig. 8. Post-gonococcal stricture in the bulbar urethra extending to the sphincter level. (*a*) Preoperative urethrogram. Stricture dilated regularly for 14 years. Balanitis xerotica obliterans of the external urethral meatus. (*b*) Following a full length urethroplasty, the patient was incontinent, which was difficult to assess as he developed a compulsive retropulsion, having to be guided into out-patients walking backwards! Postoperative urethrogram, however, revealed a large diverticulum of the scrotal inlay secondary to meatal stenosis. Incontinence and urethral redundancy improved by meatoplasty. Curiously, compulsive retropulsion has also resolved.

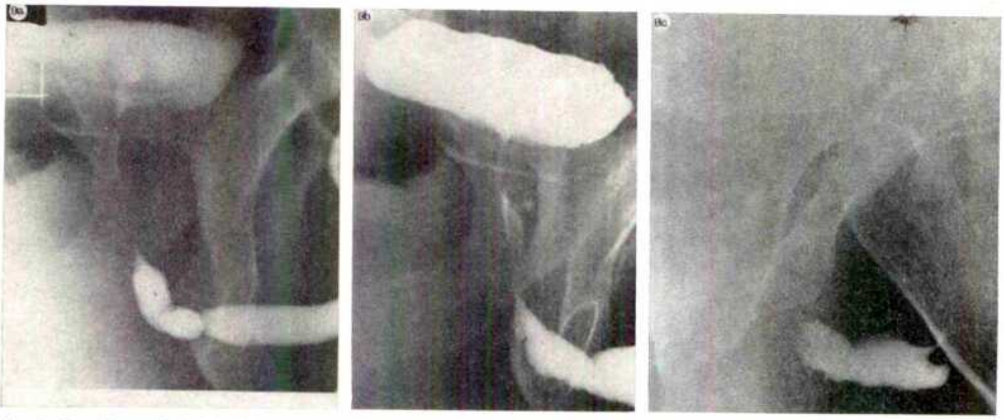


Fig. 9. Pooling of fluid within the urethra. (*a*) Urethrogram showing traumatic bulbar urethral stricture following cystoscopy when a child. (*b*) Postoperative urethrogram following a submembranous scrotal inlay. The urethral calibre is a little large. (*c*) X-ray taken 10 minutes after voiding, showing contrast retained within the closed urethroplasty accounting for slight post-micturition dribbling and retained ejaculate.

Impaired Ejaculation and Impotence. Following closure, 4 patients admit to impaired ejaculation, due to pooling of the ejaculate within the new urethra (Fig. 9).

One patient became impotent following closure of his urethroplasty and another feared intercourse because of pain in the penis on ejaculation.

Because of this even small risk of impaired ejaculation after urethroplasty, I am reluctant to do a scrotal inlay urethroplasty on a young man who is able to have normal intercourse and has not completed his family, provided that the stricture can be reasonably controlled with infrequent bouginage.

Hairy Stones. This complication was found in 2 patients at the time of their scrotal inlay, 1 having had a previous Johanson urethroplasty and the other a repair of a hypospadias. In both cases, a recurrent urethral stricture had developed and the reconstructed urethra had been irregular and redundant, predisposing to stasis, infection and stones.

By depilation of the inlaid scrotal skin and attempts to reconstruct a smooth urethra of normal circumference, problems arising from growth of hair on the scrotal flap have so far been avoided.

Restenosis. In the period of the review there has been no restenosis of the new tubed urethra at the site of the previous posterior urethrostomy opening. One case had to be re-explored 12 weeks after closure due to stenosis at the site of the previous anterior urethrostomy opening. At the interval review, there had been "tacky" adhesions at this ostium which were wrongly judged to be innocuous. This emphasises the importance of not hurrying the review stage and that if in doubt, the urethroplasty should not be closed at that time.

Is scrotal inlay urethroplasty ever impossible?

Two patients outside this series with urethral strictures and urinary penile and scrotal fistulae were unsuitable for a scrotal inlay urethroplasty, due in 1 case to almost total distortion and scarring of the scrotum (Fig. 10), and in the other to severe fixed bilateral adductor deformities of osteo-arthritic hip joints preventing operative access to the perineum.

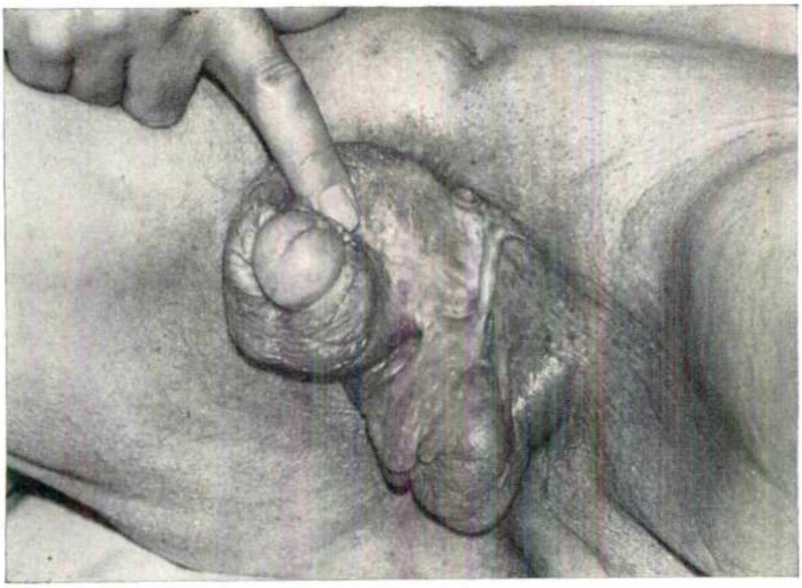


Fig. 10. An 80-year-old with multiple urethral scrotal fistulae for 40 years producing a grossly distorted penis and scrotum. Treated by amputation of the penis and scrotum with permanent perineal urethrostomy.

Comment

The Turner-Warwick scrotal inlay urethroplasty is considered to be a good and successful operation requiring attention to operative detail and judgement in the staged management of these cases.

The patient must appreciate that the review period cannot be hurried and that freedom from later dilatation depends on the establishment of a stable scrotal inlay.

Post-micturition dribbling and impaired ejaculation due to pooling of small volumes of urine or seminal fluid within the new tubed urethra have been minor complications in a small number of these cases.

The use of fine Dexon absorbable sutures for all stages of the urethroplasty is considered a significant technical advance. In the small number of patients with longstanding strictures requiring several readjustments of the scrotal inlay or electing not to proceed to closure, a feature is their appreciation at being relieved from a life revolving around their next visit to a dilatation clinic or the time for changing their permanent suprapubic catheter and a willing acceptance of having to sit to void.

Summary

The use of the Turner-Warwick scrotal inlay urethroplasty has been reviewed in 37 cases, of whom 25 have been completed with closure of their urethroplasties.

The patients have been delighted with their micturition even during the review stage but slight post-micturition dribbling and impaired ejaculation have been reported in a few cases.

The use of fine Dexon absorbable sutures throughout all stages of the urethroplasty has been recommended.

I wish to express my gratitude to Richard Turner-Warwick for initiating me into this technique of scrotal inlay urethroplasty.

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The Urethral Pressure Profile: Theoretical Considerations and Clinical Application

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The urethral pressure profile is a graphical record of pressure within the urethra at successive points along its length. Enhorning (1961) was the first to define urethral pressure with regard to incontinence. It follows that continence must be maintained if the intra-urethral pressure (I.U.P.) is greater than the intra-vesical pressure (I.V.P.). This pressure difference is termed the urethral closure pressure (C.P.).

One of the first methods of measuring urethral pressure was described by Langworthy and his colleagues (1940) in cats. This method involved the retrograde instillation of fluid into the urethra until the pressure was sufficient to overcome the sphincter resistance and force fluid into the bladder. Bors (1948) applied the same technique to humans, measuring the pressure directly on a vertical manometer tube. Fluid-filled pressure balloons have been favoured as a method of measuring urethral pressure, but would appear to have the disadvantage of measuring pressure over a finite length of urethra, equivalent to the length of the balloon, rather than pressure at consecutive points. Barnes (1940), Youssef and Mahfouz (1956), Enhorning (1961) and recent British workers, Caldwell *et al.* (1968) and Riddle, Hill and Wallace (1969), used balloon techniques with satisfactory though divergent results.

The simplest method of measuring pressure within the urethra is the urethral pressure profile technique of Toews (1967) and Brown and Wickham (1969). This technique measures pressures at consecutive "points" along the whole length of the urethra, the size of these "points" being equivalent to the diameter of the side-holes in the cannula. In the early stages of development of this technique, the profiles were roughly recorded and it was not until the introduction of the catheter position transducer (Harrison and Constable, 1970) that superimposition of consecutive readings in the same patient was possible, together with an accurate measurement of urethral length, recording of the maximum pressure rise within the urethra, and localisation of specific urethral lesions in relation to the fixed points of the bladder neck and the external meatus. An alternative to the catheter-position transducer method of recording is the mechanical withdrawal device which has been described elsewhere (Malvern and Edwards, 1972).

In this paper we set out to examine the urethral pressure profile recordings in normal and in pathological conditions, and to analyse the results obtained.

Patients

227 consecutive female patients were studied. The patients were investigated in the Incontinence Unit of the Institute of Urology, at the Institute of Obstetrics and Gynaecology and in the Department of Urology at the London Hospital.

The patients were divided into 3 groups. The first group consisted of normal patients, who were volunteers about to undergo dilatation and curettage, tubal ligation or infertility investigations. They had no symptoms referrable to the lower urinary tract and in none could urinary loss be demonstrated on coughing, either in a dorsal or a standing position when the bladder contained 120 ml of saline.

The second group consisted of patients with detrusor dysfunction. The majority of these complained of urgency and frequency of micturition, and some were incontinent. All the women in this group had abnormal cystometrograms; some had uninhibited bladders, some atonic bladders, some showed apparently normal bladders but uninhibited voiding contractions occurred when the bladder was full, and a few had non-contractile bladders. These four abnormal cytometric patterns have been described elsewhere and in detail by one of us (Edwards, 1973).

The third group consisted of patients with symptoms of stress incontinence, in whom we were able to demonstrate urinary loss coinciding with a cough in the standing or dorsal positions, when 120 ml of saline had been instilled into the bladder. Alternatively, stress incontinence was demonstrated on micturating cystourethrography. All patients in this group had normal cystometrograms.

Method

Normal saline at body temperature was infused through a profile cannula (Porges Ltd., Paris) at a constant rate of 2 ml per minute. The pressure was measured with a standard physiological transducer system, and the profiles recorded on a standard electrical pen-recorder (Smith Servoscribe 2 and Servoscribe M). The method of catheter withdrawal used was either that of Harrison and Constable, or the mechanical method. The apparatus used is shown diagrammatically in Figures 1 and 2.

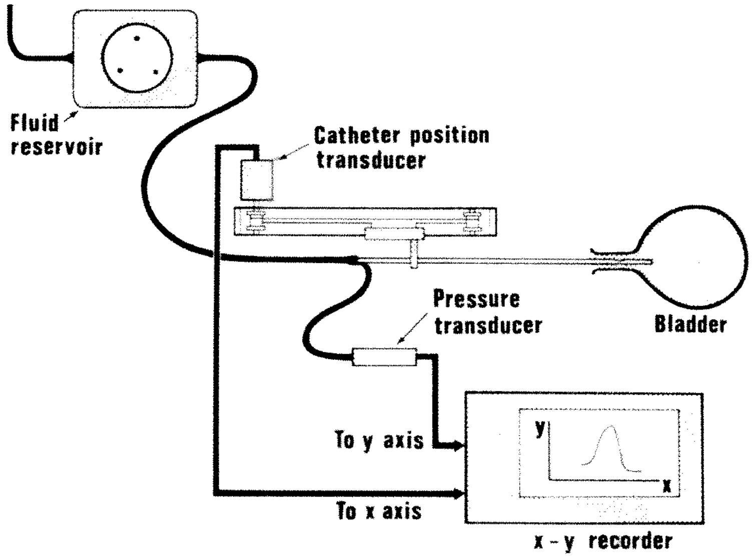

Fig. 1. Apparatus employing the Harrison and Constable position transducer method of recording catheter withdrawal. A non-pulsatile pump is used for instilling the fluid rather than a barrel-syringe as described originally.

Definition of Terms

A diagrammatic representation of the female urethral pressure profile is shown in Figure 3. The following were determined:

(*a*) the intravesical pressure;
(*b*) the maximum urethral pressure, occurring in the mid-urethral zone;
(*c*) the exit pressure occurring when the side-holes of the cannula emerged into the outside air;
(*d*) the maximal sphincter pressure, or profile amplitude, obtained by subtracting (*a*) from (*b*);
(*e*) the urethral length, expressed in centimetres.

Parameters (*a*) to (*d*) inclusive were expressed in centimetres of water pressure.

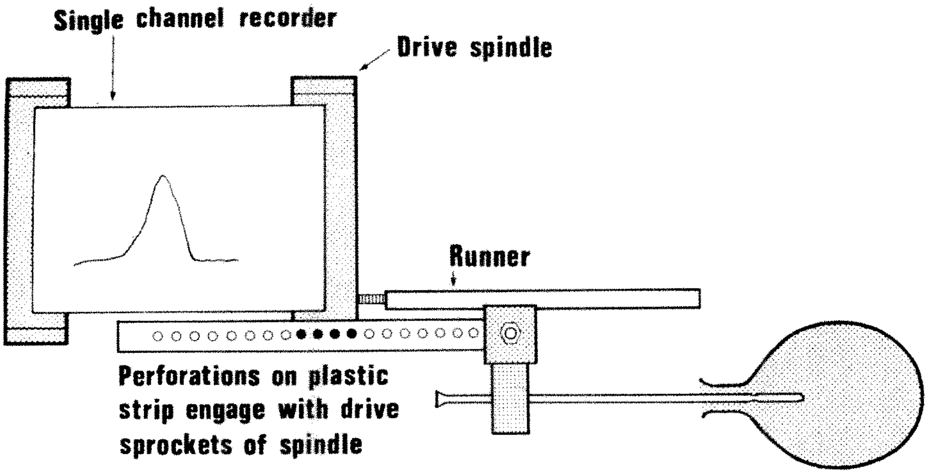
Single channel recorder
Drive spindle
Runner
Perforations on plastic strip engage with drive sprockets of spindle

Fig. 2. Apparatus employing the mechanical drive method of catheter withdrawal in which the catheter is linked with the spindle driving the chart paper.

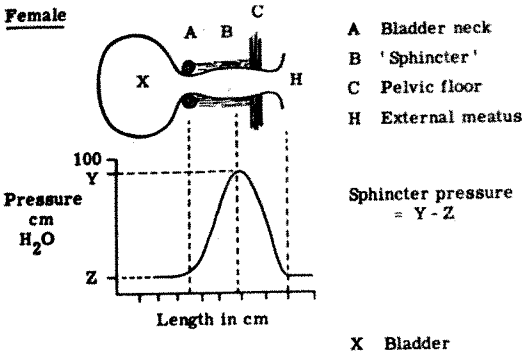

Fig. 3. Diagrammatic representation of the urethral pressure profile. The intravesical pressure = Z cm H_2O. The maximum urethral pressure = Y cm H_2O. The sphincter resistance which = (Y-Z) cm H_2O is recorded at level B.

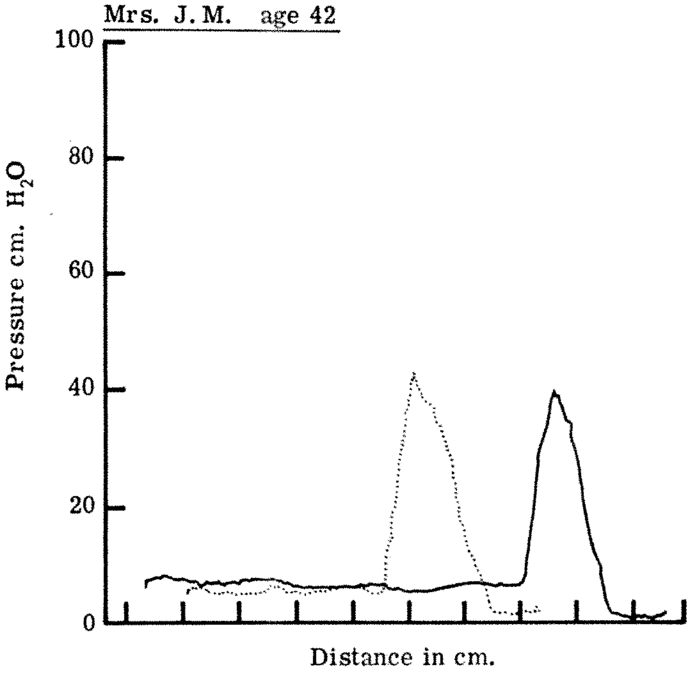

Fig. 4. Urethral pressure profile recorded with two different catheters. To show reproducibility of recordings made with different sized cannulae. —— = 10 Ch cannela; .... = 7 Ch cannula.

Sources of Error

1. *Alterations in Catheter Size*

Catheters of 3 sizes were used in an experiment to assess the variations in the results obtained. The sizes were 8, 10 and 12 Charrière, and no difference was seen between the observations made in the same patient with any of the catheter sizes (Fig. 4).

2. *Alterations in the Perfusion Rate*

It was found that the profile amplitude was reduced when the infusion rate was less than 2 ml per minute. Above this critical infusion rate, and as high as a flow rate of 20 ml per minute, the profile did not appear to alter significantly in its contour or amplitude (Fig. 5).

3. *Rate of Catheter Withdrawal*

Rapid withdrawal of the catheter from the urethra was found to result in low recordings of urethral pressure. However, this error was eliminated at withdrawal rates of less than 20 cm/min. If the catheter is removed manually rather than mechanically, we would recommend that several

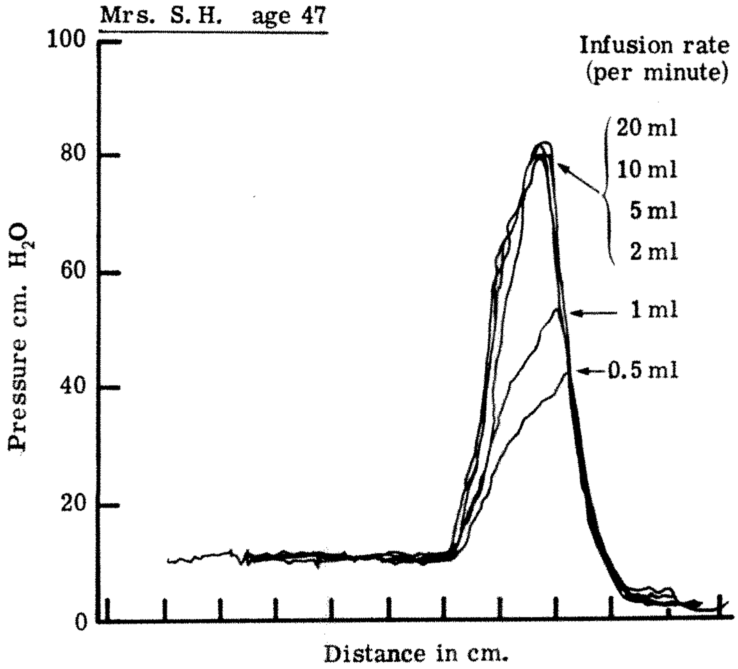

Fig. 5. Urethral pressure profile showing variation in amplitude.

recordings should be carried out slowly to ensure that the readings are consistent. This is particularly important before proceeding to investigations which might alter the profile characteristics; for example, the application of incontinence-preventing devices (Edwards and Malvern, 1972, 1973).

4. *The Effect of Anaesthesia*

Profiles were undertaken under 3 sets of varying conditions:

(*a*) without any anaesthesia, the catheter being inserted simply by lubrication with standard water-soluble jelly;
(*b*) with local anaesthesia, where the urethra was filled with a standard antiseptic-anaesthetic jelly;
(*c*) under light general anaesthesia, without administration of muscle relaxants.

It was found that there was no significance between the profiles recorded under any of the 3 different conditions (Table I).

5. *Patient Position*

Recordings were usually obtained with the patient in the dorsal position with the knees drawn up, or if undertaken under general anaesthesia with the patient in the standard lithotomy position. They were, however, also carried out with the patient in the erect position, with the feet slightly apart and showed the following changes when compared with those in the supine position:

(*a*) an increase in the resting bladder pressure;
(*b*) an increase in the maximum intra-urethral pressure.

The subtracted difference between these 2 increased values represented a profile amplitude of the same mangitude as that recorded with the patient supine (Fig. 6).

6. *Reproduction of Results*

It was found that the urethral pressure profile was reproducible when repeated time and again in the same patient at the same examination. It was also found that there was no significant difference between the profile estimations carried out on the same patient at varying time intervals, the maximum of which was 6 months.

Results

The 227 patients studied were divided into 3 groups as shown in Table II.

Table I

Effect of General Anaesthesia on the Profile

	Effect on Amplitude (number of cases)			
	Increase >5 cm H_2O	Decrease >5 cm H_2O	No Change ± 5 cm H_2O	Total
General				
Sphincter weakness	20	22	20	62
Detrusor dysfunction	4	18	6	28
Number studied under both L.A. and G.A.				90

	Profile Amplitude (cm H_2O)	
	Sphincter Weakness	Detrusor Dysfunction
Statistical Analysis		
L.A. mean	38·0	50·9
S.D.	±18·0	±24·4
G.A. mean	35·4	38·8
S.D.	±17·6	±18·0
Standard error of difference	3·197	5·73
t	0·813	2·11
P	>0·1	>0·05

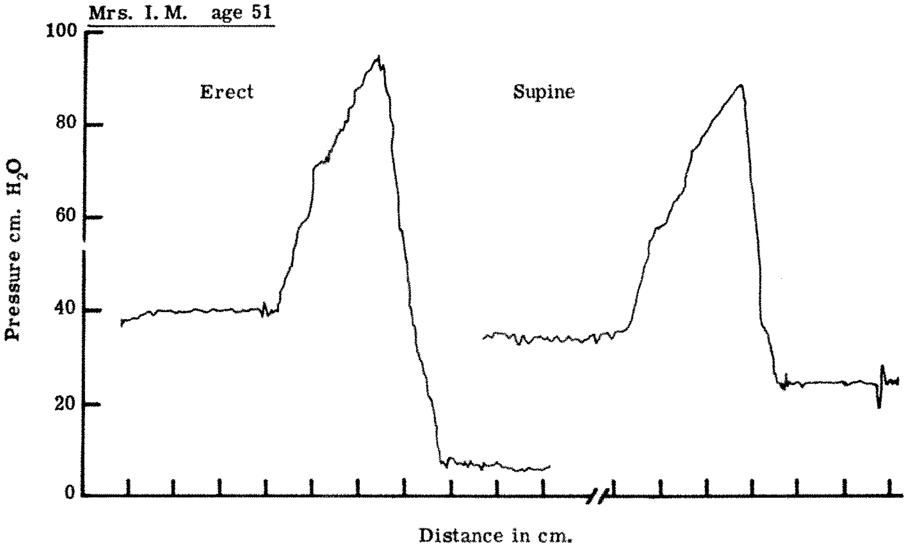

Fig. 6. Urethral pressure profiles obtained with the patient erect, and supine. There is no significant difference between the amplitude in the two cases. That on the left, the erect profile, has been drawn at the side of the supine profile on the right for easier comparison. The original tracings showed equal pressures at the end-points of the test.

Amplitude

The mean profile amplitude was calculated in each of the groups which were subdivided by age into decades. The results obtained are shown in Table III. It was found that the normal profile amplitude was higher than the profile amplitude in both abnormal groups in all decades of life, and with the exception of the first decade, the profile amplitudes of patients with detrusor dysfunction was higher than that of patients with sphincter weakness. The difference between the profile amplitudes recorded in all 3 groups was statistically significant in all decades, the level of significance falling as the age increased (range $P < 0{\cdot}001$ to $P < 0{\cdot}01$). The trend was for the profile amplitude to fall in all groups as the age increased, and because of this, further analyses were undertaken.

Regression Analysis

The normal patients and those with sphincter weakness were analysed statistically by the regression method, the profile amplitude being correlated with the patients' ages. In the case of the normal patients and the patients with sphincter weakness, a negative linear correlation was seen,

Table II

Patients Studied

Normal	69
Sphincter weakness	103
Detrusor dysfunction	55
Total	227

and the statistical significance of these correlations was high ($P < 0{\cdot}0005$). However, the mean age of the group of normal patients was lower than that of the patients with sphincter weakness and the statistical significance of this difference was high ($P < 0{\cdot}005$). Therefore, patients between the ages of 30 and 60 years only were studied further, and in these patients the difference between the mean ages of the groups was not statistically significant. However, the significance of the linear correlation between amplitude and age was maintained (Figs. 7 and 8).

Table III

Mean Urethral Profile Amplitude (in cm H_2O)

	Age-groups (Years)							
Patients	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71+
Normal	84*	...	83	73	51	47	42	54
Sphincter weakness	58	30	47	52	40	34	24	26
Detrusor dysfunction	21*	53	70	63	61	36	39	36

* Only 1 patient in these groups.

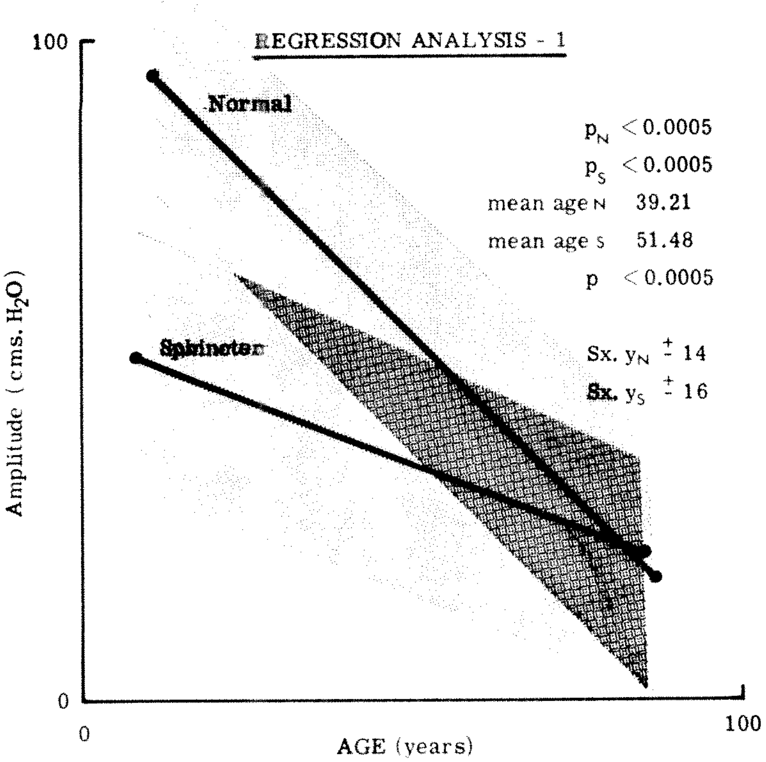

Fig. 7. Regression curves for the profiles of patients with sphincter weakness and normal patients. In both cases there is a negative linear correlation between the patients' ages, and the profile amplitude. The shaded portions represent one standard deviation above and below the mean. There is a significant difference between the mean age of the patients in the 2 groups.

Urethral Length

Analysis showed that in the 3 groups studied there was no significant difference in mean urethral length (Table IV).

Table IV

Urethral Length

Patients	Number	Mean Length (cm)	Standard Deviation
Normal	28	3·55	±0·64
Sphincter weakness	69	3·47	±0·9
Detrusor dysfunction	57	3·71	±1·05

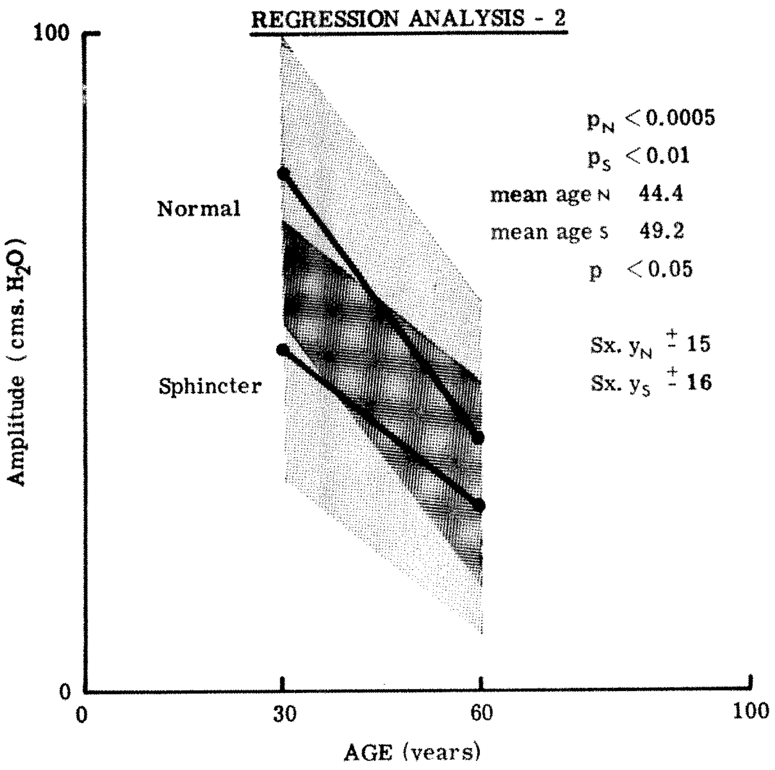

Fig. 8. A smaller number of patients has been studied to eliminate the difference between the mean ages of patients in the 2 groups. The negative linear correlation between age and profile amplitude is maintained.

Discussion

The results of this study have shown that the urethral pressure profile is a method of investigation which is subject to little in the way of experimental error. The recordings made are consistent irrespective of catheter size, infusion rate (subject to limit expressed) patient position and the use of local or general anaesthesia.

The urethral pressure profile amplitude appears to fall as the patient's age increases. This trend is more marked in normal patients than in those with sphincter weakness, and this may be because patients with sphincter weakness were diagnosed on an all-or-none basis, and the severity of their condition was not taken into account during the present study. On inspecting the regression curves, and noting the standard errors obtained, it will be seen that the shaded portions represent one standard deviation from the mean, and overlap as the patients' ages increase. These overlapping areas represent the zones where the data points merge and it would be reasonable to conclude that, when this happens, the diagnostic importance of the test is obscured. However, the estimation may be used as a diagnostic index in defining the presence or absence of sphincter weakness subject to the limitations already described. Taking 1 standard deviation below the mean of the normal regression curve, a formula may be calculated as follows:

$$\underset{(\text{cm } H_2O)}{\text{Amplitude}} = 92 - \text{patient's age in years.}$$

If the observed profile amplitude is less than this calculated value, the diagnosis of sphincter weakness may be established, subject to an accuracy of 66%. The accuracy will, of course, be much higher in the younger patients.

With regard to patients with detrusor dysfunction, we have not found that the urethral pressure profile estimation has been of any diagnostic importance, and have preferred to rely on the demonstration of abnormalities on cystometry.

Summary

A simple technique for the urethral pressure profile estimation has been studied and evaluated. The estimation would appear to be relatively free of sources of error.

The diagnostic importance of the test in distinguishing between the normal patient and the patient with sphincter weakness has been discussed.

We should like to thank the consultants at the Shaftsbury Hospital, London Hospital and Chelsea Hospital for Women for referring patients to us, and in particular Professor C. J. Dewhurst of the Institute of Obstetrics and Gynaecology and Professor J. P. Blandy of the London Hospital.

One of us (L. E.) carried out this work as part of the requirement for the M.Chir. degree of the University of Cambridge.

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The Role of Some Tryptophan Metabolites in Certain Diseases of the Genito-Urinary System[1]

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Tryptophan is one of the essential amino acids and its metabolism and end products have been studied intensively. Four possible metabolic pathways in the metabolism of tryptophan are known, but of these, the fourth appears to have most relevance to the study of disease of the human genito-urinary tract. Boyland (1958) indicated that 3-hydroxy-kynurenine and 3-hydroxy-anthranilic acid, which are products from tryptophan via the fourth (kynurenine) pathway, might cause malignancy of the bladder in man. Tryptophan is unique among the essential amino acids in that it contains an indole nucleus and in the body is converted into other biologically important compounds such as nicotinic acid, serotonin, certain pigments and alkaloids.

The fourth metabolic pathway consists of a series of enzyme catalysed reactions which lead to the formation of nicotinic acid (Dalgliesh, 1960) and in this process kynurenine is the key substance. Vitamin B6 is of special importance in this pathway and its deficiency leads to accumulation of certain metabolites such as kynurenine, 3-hydroxy-kynurenine, kynurenic acid and xanthurenic acid (Dalgliesh, 1956). Thiamine, riboflavin and vitamin C are also required for certain stages in this pathway (Dalgliesh, 1956; Henderson, Koski and d'Angeli, 1955; Schlegel *et al.*, 1969). The fourth pathway appears to be the most important in relation to bladder cancer, urinary calculus, and urinary infection. Boyland and Watson (1956) induced bladder carcinoma in mice by inserting pellets containing 3-hydroxy-anthranilic acid in the bladder. Allen *et al.* (1957) and Bryan, Brown and Price (1964) suggested that pellets of other tryptophan metabolites introduced into the bladder produced a significant incidence of bladder carcinoma in mice. Higher urine concentration of 3-hydroxy-anthranilic acid and kynurenine have been found in patients with cancer of the urinary bladder when compared with urine from normal subjects or those with cancer localised to organs other than the bladder (Boyland, 1958).

The urinary tryptophan metabolite 3-hydroxy-anthranilic acid has been estimated by paper chromatography in patients with bladder cancer (Quagliariello *et al.*, 1961) and by a colorimetric method (Tompsett, 1959). All these workers found that patients with cancer of the bladder excrete more 3-hydroxy-anthranilic acid than those without tumours. Perissinotto, Benassi and Allegri (1964) observed that 17 out of 28 patients with renal tumour secreted a higher level of kynurenine alone or with 3-hydroxy-kynurenine and 3-hydroxy-anthranilic acid. Studies by Gholson *et al.* (1959) suggested that serine could be derived from the side chain of tryptophan. Glycine and glyoxylic acid in turn may be derived from serine (Weinhouse, 1955). Gershoff and Prien (1960) and Faber *et al.* (1963) reported an increased excretion of oxalate after administration of a tryptophan load to human subjects. This work suggested that tryptophan might be a precursor of urinary oxalate.

In bladder schistosomal infestation the ortho-amino-phenol derivatives were twice the normal level while in bladder cancer with schistosomal infestations the level was almost 8 times normal (Khalafallah and Abdul-Fadl, 1964).

This paper deals with the measurement of kynurenine, 3-hydroxy-kynurenine, anthranilic acid and xanthurenic acid in the urine of normal people and those suffering from bladder cancer, urinary calculus, urinary infection and a number of other diseases of the genito-urinary system.

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[1] This work formed part of a Ph.D. thesis accepted by the University of Dundee.

Material and Methods

The amount of xanthurenic acid, anthranilic acid, kynurenine and 3-hydroxy-kynurenine was measured in each of two 24-hour collections of urine from 10 normal people, 11 patients with urinary bladder malignancy, 1 patient with renal papillary transitional cell carcinoma, 1 with renal clear cell carcinoma, 1 with ovarian carcinoma, 1 with prostatic carcinoma, 15 with urinary tract infection, 13 with kidney and 1 with bladder stones, 5 with benign prostatic hyperplasia, 3 with ileal urinary conduits and 2 with retroperitoneal fibrosis. In addition 7 of the control group were given a loading dose of 2 g of tryptophan and the excretion of the 4 metabolites again measured.

Using basically the method of Walsh (1965) thin layer chromatography (with cellulose CC 41 as the thin layer) the 4 metabolites were separated and then identified by their fluorescence and colour reaction with Ehrlich's reagent and diazotised sulphanilic acid. The area of cellulose containing each substance was marked with a needle and the areas scraped off into individual test-tubes. For xanthurenic acid and 3-OH-kynurenine 1·5 ml of deionised water was added to each test tube and they were allowed to stand for 1 hour at room temperature. After centrifugation 1 ml of diazotised sulphanilic acid at 10°C was added to each. The optical density was read on a Unicam SP 500 spectrophotometer at 510 mμ fluorescence wavelength, immediately for xanthurenic acid and after 10 minutes at 450 mμ for 3-OH-kynurenine.

In the case of kynurenine only 1 ml of deionised water was added and the tube was allowed to stand for 30 minutes before adding 2 ml of Ehrlich's reagent. After 10 minutes the solution was centrifuged and the optical density of the supernatant read at 450 mμ fluorescence wavelength. Anthranilic acid was treated in the same way except that the eluate was incubated at 37°C for 30 minutes with sufficient urease to remove the urea before centrifuging and adding Ehrlich's reagent and that the wavelength was 470 mμ.

A linear relationship obtains between standard solutions of the pure substances and their optical density and quantities present in the experimental material can be read from suitably prepared graphs.

As 0·1 ml of urine was used for each estimation the total metabolite mg per kg body weight is readily calculated from the following:

$$\text{Metabolite in mg/kg body weight} = \frac{a \times b \times 10}{100 \times w}$$

Where

a = metabolite in micrograms/0·1 ml urine
b = 24-hour volume of urine in ml
w = body weight in kg.

Results

In Table I the effect of the loading dose of 2 g of tryptophan on the output in the urine of 4 metabolites is recorded. The output varies from 2·79% to 6·05% a marked increase compared with the unloaded output. The detailed results have already been presented (Al-Hadithi, 1971) and these are summarised in Table II—mean excretion in mg/kg/24 hours for each of the metabolites and the mean total excretion of the 4.

Discussion

Over the past 15 years many workers have reported the mean excretion of kynurenine, 3-hydroxy-kynurenine, anthranilic acid and xanthurenic acid in normal subjects with considerable variation

Table I

Percentage of Urinary Excretion by the Normal Subjects after 2 g Loading Dose of Tryptophan

Patient No.	Total %	Kyn. %	3-OH-Kyn. %	Anth. Acid %	Xanth. Acid %
1	5·57	2·46	0·93	1·25	0·93
2	2·79	1·12	1·17	0·17	0·33
3	6·05	2·66	1·1	1·09	1·2
4	3·82	1·65	1·12	0·66	0·39
5	3·7	1·08	0·46	0·91	1·31
6	3·21	1·1	0·49	1·4	0·22
7	4·34	1·18	1·08	1·36	0·72

Table II

Mean Excretion in mg/kg of each of the 4 Metabolites and Mean Total Excretion in each of the Clinical Groups. Figures in Brackets indicate Number in each Group.

	Metabolite				
Clinical Group	Kyn. Mean Excretion mg/kg	3-OH-Kyn. Mean Excretion mg/kg	Anth. Acid Mean Excretion mg/kg	Xanth. Acid Mean Excretion mg/kg	Mean Total Excretion of 4 Metabolites mg/kg/24 hours
Control (10)	0·09	0·097	0·10	0·066	0·353
Genito-urinary malignancy (15)	0·533	0·198	0·369	0·068	1·168
Urinary tract infection (15)	0·133	0·039	0·132	0·024	0·328
Calculus (14)	0·159	0·073	0·143	0·023	0·398
Prostatic hyperplasia (5)	0·283	0·054	0·117	0·028	0·482
Ileal conduit (3)	0·193	0·10	0·177	0·039	0·509
Retroperitoneal fibrosis (2)	0·842	0·125	0·22	0·048	1·235

in their results. If, however, weight is taken into account and the output expressed in mg per kg body weight, the total excretion of the 4 metabolites in the control series has the narrow range of 0·168 to 0·44 mg per kg body weight. The exception was a patient on the contraceptive pill and oestrogen is known to raise the excretion rate (Rose, 1966*a* and *b*). Neither age nor sex appeared to influence the output in our series. This confirmed the earlier finding of Späcek (1955).

In the group of 7 patients given a loading dose of 2 g D.L. tryptophan 2·79% to 6·05% of the dose was excreted in the form of the 4 metabolites being studied (Table I). This corresponds closely to the finding of Brown and Price (1956) where the range was 1·7% to 6·6% with the same loading dose and to those of Boyland and Williams (1956) who used 10 g. D.L. tryptophan as their loading dose and recovered about 5% in the form of the 4 metabolites.

Variation in the output of the 4 metabolites was relatively small in the control group, in infection, in calculus disease and in those with ileal conduits. The latter were the most consistent excretors and we have found no reference in the literature to excretion of tryptophan metabolites in human ileal conduits. In malignancy and prostatic hyperplasia there was a greater variation in output. Five of the 11 patients with bladder carcinoma excreted 20·5 to 120·2 mg kynurenine in 24 hours and 4 of them excreted 17·7 to 132·1 mg anthranilic acid daily. All the patients excreted only a small amount of xanthurenic acid. Boyland and Williams (1956) studied 10 patients with bladder cancer and found increased excretion of kynurenine (average 68·4 mg per 24 hours) anthranilic acid (average 88·92 mg per 24 hours) and 3-hydroxy-kynurenine (average 13·0 mg per 24 hours). Quagliariello (1961) also found that 8 out of 47 patients with bladder neoplasm excreted a large quantity of kynurenine. In our series the increased excretion of tryptophan metabolites is not peculiar to renal and vesical neoplasm and prostatic hyperplasia. We found increases of varying degree in patients with urinary infection and urinary calculi. In the calculus group 6 out of 14 patients excreted abnormal amounts of kynurenine, 1 of these had oxalate and another struvite (magnesium ammonium phosphate) as the principle constituent in the stone. This raises the question of the relation of tryptophan break down to oxalate excretion. Gershoff and Prien (1960) and Faber *et al.* (1963) all reported increased excretion of oxalate after giving a tryptophan load to human subjects.

Having considered the control and experimental groups one or two problems remain in relation to interpretation of the results. When the mean excretion in mg per kg body weight of the 4 metabolites was examined, this showed an increase in some cases of cancer, calculus, and infection but this increase was not consistent for any one metabolite. At first this is puzzling but attention has been drawn to the multiplicity of pathways in tryptophan metabolism. Because of this multiplicity there may well be pathway switching in the course of 24 hours and from day to day. In no condition studied has there been a constantly increased excretion of any of the 4 metabolites examined. This might suggest that:

(*a*) Variation in tryptophan metabolite excretion is not a reliable diagnostic guide and
(*b*) that tryptophan metabolites are not the most helpful to study.

This present work confirms that of others in showing a definite increase in tryptophan metabolites excretion in transitional cell neoplasm of the bladder and elsewhere, and that increased excretion occurs sporadically in calculus disease, prostatic hyperplasia, urinary tract infection and possibly retroperitoneal fibrosis.

As yet therefore tryptophan metabolite excretion is not a reliable diagnostic guide but study of this excretion is proving helpful in bladder neoplasm. Our work indicates that more selection in calculi and urinary tract infection and probably also in bladder neoplasm, might lead to further valuable information.

Summary

Thin-layer chromatography (qualitative and quantitative) was used to examine the excretion of 4 tryptophan metabolites, kynurenine and 3-hydroxy-kynurenine, anthranilic acid and xanthurenic acid.

The control group showed a small range of variation from day to day and from person to person, except for one who was on the contraceptive pill. She showed a marked increase in the amount of the metabolites excreted.

The excretion was increased in a proportion of the kidney and bladder neoplasm patients. In the calculus cases, 2 showed a marked rise, while of the patients with prostatic hyperplasia 1 had a very high excretion as did 1 of the cases of retroperitoneal fibrosis.

High excretion can occur in a variety of conditions but as yet is no aid to diagnosis.

Very many people have helped me in many ways and I thank them all collectively. I would, however, mention Mr J. Grieve, Department of Urology, Ninewells and Associated Hospitals, for acting as my supervisor and mentor. Professor Sir Donald Douglas for facilities in the University Department of Surgery, the Eastern Regional Hospital Board for accommodation and facilities in the Clinical Investigation Unit, Maryfield Hospital, the clinical and technical staff of the latter unit and Dr Peter Mitchell and the staff of Clinical Chemistry, Maryfield Hospital for the loan and use of equipment, and Dr J. P. Mellon and his staff for introducing me to practical thin layer chromatography.

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The Author

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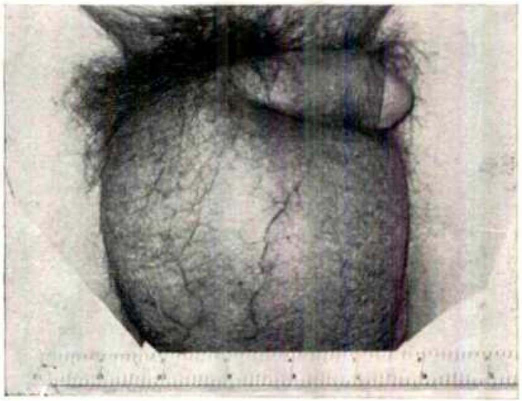
British Journal of Urology (1974), **46**, 343

Short Case Reports

Pneumoscrotum Complicating Pneumothorax and Surgical Emphysema

A man of 60 with a proved bronchial carcinoma developed a right-sided pneumothorax on 16th April 1973. This was treated with an indwelling Argyll catheter placed in the second intercostal space in the mid-clavicular line and connected to an underwater-seal drain. Two days later marked surgical emphysema was detected over the chest wall and extending to the abdomen. The tube came out and treatment was continued with a Malecot catheter in the right axilla. Six hours after this he complained of swelling and discomfort in the scrotum. The entire scrotum was found to be distended to 12·5 cm diameter. It was not tender and it transilluminated readily. Aspiration of the air was easily performed through a small needle, and the scrotal sac returned to normal. It subsequently refilled, but as it caused no discomfort aspiration was not repeated. The patient's general condition rapidly deteriorated and he died on 10th May 1973.



Scrotum distended with air.

Gaseous distension of the scrotum is not common. The majority of cases are associated with pneumoperitoneum and in them the air is within the tunica vaginalis, presumably reaching it through a patent processus vaginalis. In a minority of cases (including the case presented in this paper) the air is not in the tunica vaginalis. Nelson and Laidig (1962) described "emphysema" of the scrotum following drainage of the chest and Keyes (1912) reported "pneumoscrotum" following nephrostomy. "Emphysema" is probably a misleading term because air in the scrotum may not give rise to crepitation (Bush and Nixon, 1969). It is suggested that the air in these cases passes along the inguinal canal in the space between the deep subcutaneous fascia and the spermatic fascia.

I would like to thank Dr B. S. Mantell for his help in the preparation of this case report and Dr W. F. Wheeler for taking the photograph.

G. J. Archer,
London Chest Hospital
(now at Leeds General Infirmary).

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Broncho-Pleuro-Colonic Fistula Secondary to Pyonephrosis

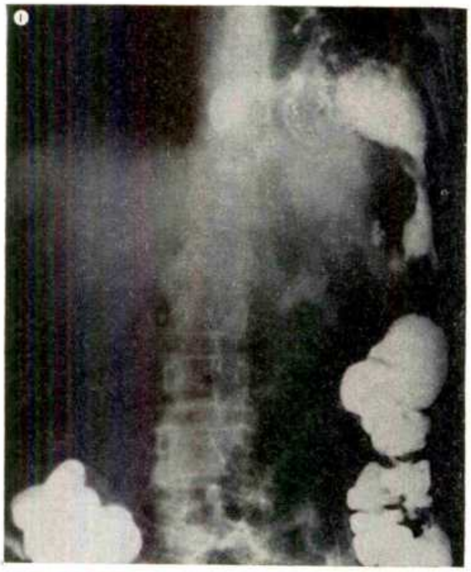
Case Report. A woman aged 75 years gave a 2-month history of change of bowel habit, night sweats and loss of weight. On examination there were signs of a left pleural effusion. The sputum was black, viscid and foul-smelling. Haemoglobin 10 g/100 ml, W.B.C.s 10,700 (78% neutrophilia). Mid-stream urine: 80 W.B.C./H.P.F.; culture sterile. X-ray of chest revealed collapse of the left lower lobe and an associated fluid level. Barium enema showed no abnormality of the descending colon but was interrupted by the patient's coughing up barium. Subsequent screening showed that the splenic flexure communicated with the left lower bronchus through an abscess cavity. X-rays of renal tract and I.V.P. showed a large staghorn calculus in a functionless left kidney (Figs. 1 and 2).

It was decided to operate with the limited objective of closing the bowel fistula and draining the abscess. Laparotomy revealed a large left subphrenic abscess containing faeculent pus. It communicated through the diaphragm with the left lower bronchus. The splenic flexure of the colon (into which the fistula opened) and the spleen were resected. The patient died 3 weeks later. Postmortem examination showed that the bowel anastomosis was sound. There was bilateral faecal pneumonia. A left calculous pyonephrosis communicated with the subphrenic abscess. The pelviureteric junction was completely stenosed. The piece of colon resected had been shown to be normal apart from the fistula in it.

Only 5 previous cases of broncho-pleuro-colonic fistula have been reported and in none of them was pyonephrosis the cause.

We are indebted to Dr D. J. Woodgate and Mr H. G. Naylor, under whose care the patient was admitted, for their help in presenting this case.

T. H. BAKER,
Orsett Hospital, Essex.
P. M. ALI,
Basildon Hospital, Essex.



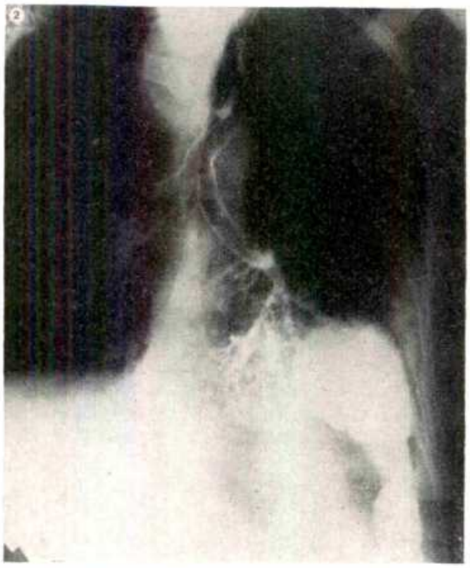


Fig. 1. Barium enema showing a communication between the splenic flexure and the left lower lobe bronchus via an abscess cavity. The stag-horn calculus is also seen.

Fig. 2. Further film to show the fistula. The deviation of the trachea was caused by a large retrosternal goitre.

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Appendiculo-Vesical Fistula with Stone in the Appendix

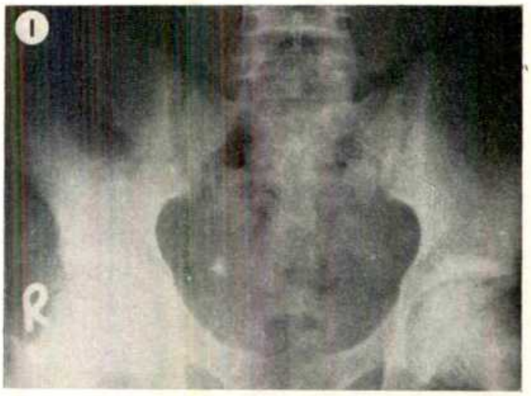
A youth aged 15 years was admitted to hospital in February 1971 complaining of episodes lasting for 7 to 10 days of haematuria and pyuria for the past 1½ years. Six months previously he had developed pain in the right iliac fossa and had been very seriously ill for about 2 weeks, but had not sought medical advice.

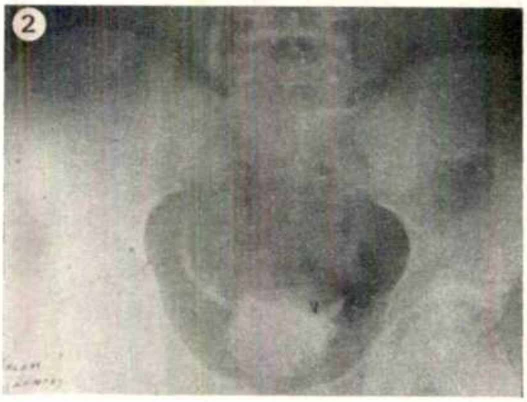
On physical examination he looked ill and pale. There was vague tenderness in the right iliac fossa. Rectal examination was negative. Haemoglobin 60%. Total white cell count 11·88 per cu.mm. E.S.R. 24 mm in the first hour Westergen. The urine was alkaline with marked albuminuria and contained pus and red cells.

Intravenous pyelography (Figs. 1 and 2) showed an irregular opacity in the line of the lower third of the right ureter, but the upper urinary tract looked normal on both sides. At cystoscopy the bladder wall was not well visualised because of haematuria. A catheter passed up the right ureter without detecting obstruction. The retrograde pyelogram was normal.

Laparotomy showed the appendix to be adherent to the right side of the bladder. The bladder was opened and a 1 cm diameter deficiency was felt in the bladder wall covered by the appendix on the outside. The appendix was removed and the hole in the bladder wall closed.

Histological examination of the appendix showed chronic inflammatory changes. No communication between the bladder and the appendicular lumen was demonstrated. There was a brown spikey stone about 1 cm in diameter in the lumen of the appendix. Analysis showed it to be composed of calcium, magnesium, phosphate and oxalate.





Comment

The majority of appendix stones are laminated in appearance and show a variable degree of mobility on X-ray (Felson and Bernhard, 1947). The appearance and the presence of oxalate in the calculus would strongly suggest it was a primary urinary calculus which had passed into the appendix following the development of a fistula. The fistula was presumably the result of an attack of acute appendicitis and had healed over before the exploration.

I wish to thank Dr S. Shah Jehan, Department of Biochemistry, Jinnah Postgraduate Medical Centre, Karachi, for analysing the stone.

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Urology Unit,
Mayo Hospital,
Lahore,
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Reference

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Knots in the Bladder

Patient 1

A 40-year-old man presented with acute retention due to a urethral stricture which was dilated with a filiform guide and followers. Difficulty was experienced in withdrawing the filiform guide from the urethra. When it was eventually withdrawn by firm traction the filiform guide was found to have knotted on itself.

Patient 2

A 20-year-old man inserted a 90 cm long electric flex down his urethra. Neither he nor his medical practitioner could extract this. X-ray showed that the flex had knotted in the bladder and cystotomy was necessary to remove it (Fig. 1).

Patient 3

A 60-year-old man presented with acute retention of urine due to prostatic enlargement. A catheter would not pass so a polythene tube was inserted into the bladder suprapubically, using a trocar and cannula. Preoperatively the tubing could not be extracted. At transvesical prostatectomy the tubing was found to have knotted on itself (Fig. 2).

These 3 cases illustrate that any flexible tube if passed too far into the bladder can knot on itself.

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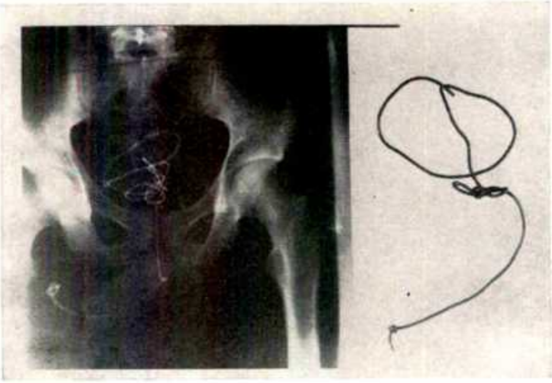

Fig. 1

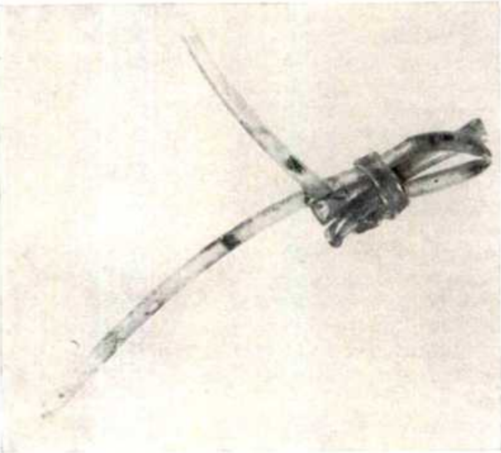

Fig. 2

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Paratesticular Liposarcoma

An obese man of 74 was admitted with acute retention due to an enlarged prostate. In addition, examination showed a large smooth, solid mass occupying both sides of the scrotum and displacing the left testicle forwards and upwards; the right testicle could not be distinguished. A scrotal swelling had been present for 10 years but no recent growth had been noted.

Following cystoscopy and transurethral resection of a malignant prostate, removal of the scrotal tumour and bilateral orchiectomy were undertaken. There was no difficulty when separating scrotal skin from the mass, and each cord was ligated at the external ring.

The specimen weighed 1,515 g and on section showed the typical appearance of a lipoma (A—Fig. 1). One aspect (C), however, was more solid and the histological appearance here was of liposarcoma (Fig. 2). In the intervening area B there could be traced the increasing cellular change from benign lipoma to sarcoma.

Malignant change of this nature has been observed in lipomata elsewhere though it is unusual. Liposarcomata arising from the cord seem very rare in recorded literature.

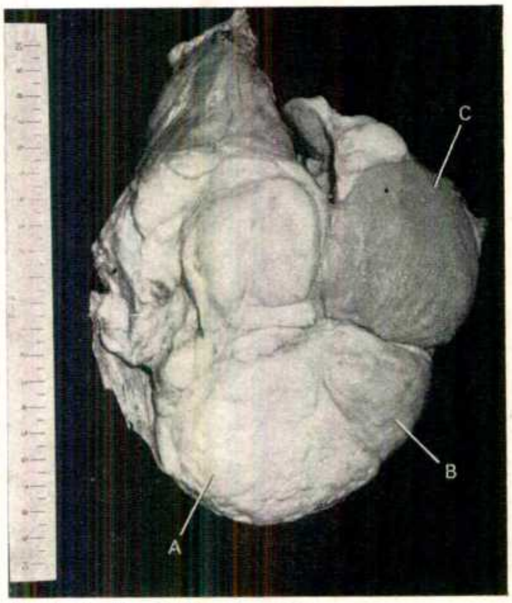

Fig. 1. The bisected tumour mass.

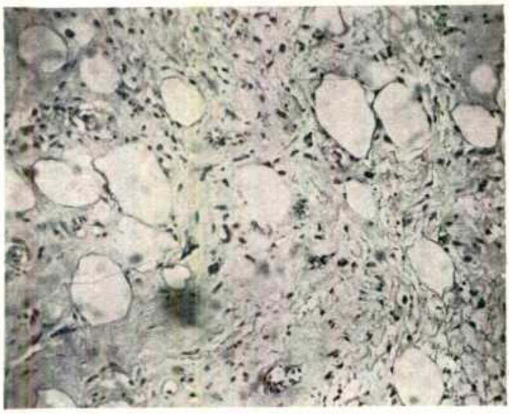

Fig. 2. Photo micrograph (×110) of portion C showing anaplastic liposarcoma. (H & E.)

I am grateful to Mr T. J. Davenport for permission to report this case, and to Dr C. F. Ross for his help and for preparing the photomicrographs.

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Greece.

British Journal of Urology (1974), **46**, 348

Dermoid Cyst of Scrotal Raphe containing Calculi

A male aged 20 complained of a swelling in the posterior part of the scrotum since birth. For the past 11 years there had been intermittent discharge from a sinus over the swelling. Micturition was normal and did not affect the discharge. There was no history of trauma. The swelling was deep to the scrotal raphe and measured 5 × 7·5 cm. It was not adherent to the deeper structures nor to the overlying skin except at the orifice of the sinus. In the swelling multiple stones could be felt. A sinogram and urethrogram defined the limits of the lesion and revealed the stones as filling defects (Fig. 1). Plain X-ray was negative and urethrogram was normal. Treatment was by complete excision of the canal and sinus with the contained calculi (Fig. 2). Histology showed the lining of the canal to be stratified squamous epithelium.

Cysts of the genito-perineal raphe are rare. We were unable to find any report of a case in which the cyst contained calculi. There may or may not be a sinus opening. These cysts result either from cell rests formed during invagination and closure of the genital folds, or they represent outgrowths of epithelium split off from the raphe after closure of the genital folds. Most of them are lined by stratified squamous epithelium. More rarely the lining is formed of cuboidal or columnar cells.

S. K. GUPTA, S. GUPTA and S. KHANNA
Varanasi, India

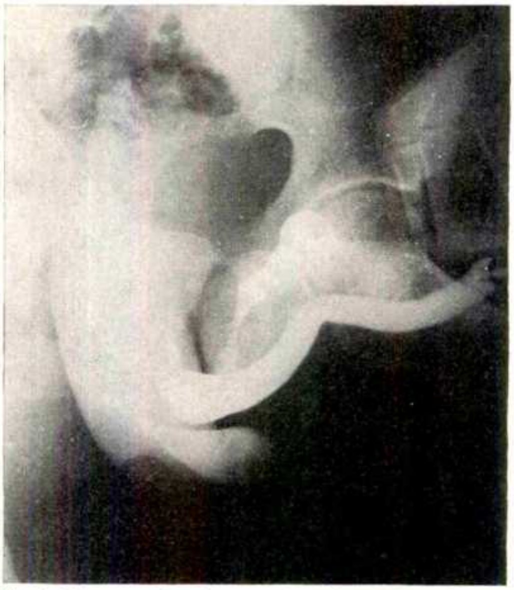

Fig. 1. Sinogram showing pear-shaped swelling and canal with multiple filling defects, together with normal urethrogram.

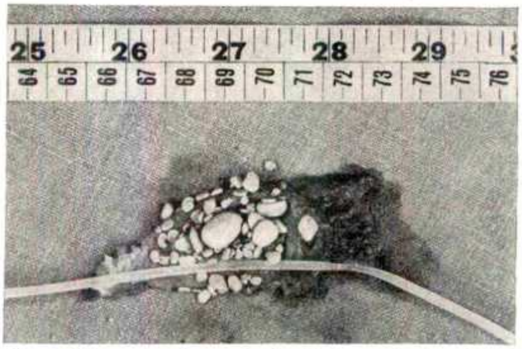

Fig. 2. The cyst and canal after being excised and laid open showing multiple calculi.

ANNOUNCEMENT

CIDA (COMITÉ INTERNACIONAL DE ANDROLOGIA)

CIDA is an international non-profit organisation formed in 1970 by the Fundacion Puigvert (Barcelona, Spain) and Professor R. Mancini (Buenos Aires, Argentina) as a forum for scientists and clinicians who have an established interest in encouraging the study of the function of the male reproductive tract (Andrology). The aim of the committee is to encourage basic and clinical research in the field and in particular to stimulate the interest of young people to become involved in the area of andrology in its broadest sense.

Individuals interested in obtaining further information are encouraged to write to the following regional representative of CIDA:

Dr J. A. van Zyl (South Africa)
Infertility Unit, Department of Gynaecology & Obstetrics, Tugerberg Hospital, Tiervlei, Cape Town, South Africa.
Dr D. M. de Kretser (Australia & S.E. Asia)
Department of Medicine, Monash University, Prince Henry's Hospital, St Kilda Road, Melbourne, Australia. 3004.
Dr J. M. Pomerol (Europe)
Institute de Urologia, Hospital de la Santa Cruz y San Pablo, Cartagena, 340-350, Apartado 24005, Barcelona-13 Spain.
Dr R. Eliasson (Europe)
Department of Physiology, Karolinska Institutet, 104 01 Stockholm, Sweden.
Dr O. Vilar (South America)
Centro de Investigaciones en Reproduccion, Facultad de Medicina, Paraguay, 2155 10° Piso, Buenos Aires, Argentina.
Dr E. Steinberger (USA & Canada)
University of Texas, Medical School at Houston, Texas Medical Centre, 6400 West Cullen Street, Houston, Texas, 77025, USA.

OMISSION

The paper on "The Single Ectopic Ureter" in the February issue (pages 3–10) contained two illustrations (Figures 4 and 5) from a previous monograph and recent paper (Les Implantations ectopiques de l'uretère—Acta Urologica Belgica, 1972, **40**, 193-504 and "Ectopie urétérale bilatérale simple", Journal d'Urologie et de Néphrologie 1973, 865-872), by Dr. C. C. Schulman without acknowledgement. We have apologised to Dr. Schulman and his publishers for the omission.

Book Review

Renal Histopathology. By Robert Meadows. 1st Edition. Pp. xii+363 with 589 illustrations. London: Oxford University Press (Oxford Medical Publications). 1973. £14·00.

In the last decade renal biopsy has compelled many pathologists and clinicians to learn the rudiments of renal pathology from scratch. They have leaned heavily on Brewer's brief but well illustrated text on *Renal Biopsy* and Heptinstall's more discursive account of *Renal Pathology*, virtually a textbook of nephrology written by a pathologist. I have no doubt that these books will now be joined by Dr Meadows's which is somewhere between its two predecessors in scope. Like them it is the work of one man with an extensive experience of renal biopsy interpretation on a very active renal unit and tireless patience in obtaining photomicrographs. In his introduction Dr Meadows makes a spirited defence of light microscopy as the main diagnostic aid of the present and the foreseeable future and he shows with a wealth of illustrative material that it is possible to demonstrate most of the important pathology of the kidney by black and white pictures of H. & E. and P.A.S. sections. My regret at the paucity of colour plates was balanced by a realisation that with many more the price would have been prohibitive. However I do feel that more use could have been made of retouched electron micrographs, which Dr Meadows employs so effectively in the section on normal anatomy, and of fluorescence micrographs.

Considering the wealth of illustration and the high quality paper which this demands the book is inexpensive at £14·00. It is not written primarily for the urologist and does not even award a chapter to obstructive uropathy. Nonetheless any urologist whose interest extends above the renal pelvis or encompasses renal transplantation will find much of interest and, if he doesn't invest £14·00 of his private income, should at least recommend the book to his postgraduate library. I have only one adverse criticism. There is a rather long gap between the end of the literary review in most chapters (1970) and the publication date. This has made inevitable the omission of some important work on clinico-pathological correlations, the renal vasculature and the role of complement. Some controversies of the 1960's such as the relationship of streptococcal infection to crescent nephritis are reproduced as if still in progress. Nonetheless a surprisingly modern classification of nephritis emerges which does not differ in many important respects from Stewart Cameron's account in the latest edition of Black's *Renal Disease*. The great value of Dr Meadows's book to the clinician is as a corrective to our natural tendency to limit our attention to the glomerulus. The first half of his book is largely devoted to a systematic account of the information that can be obtained by a study of the tubules, interstitium and vasculature, and of processes like ageing which are superimposed on renal disease. The clinician who reads it will give a more cautious, as well as a better informed, interpretation of his own renal biopsies.

D. N. S. K.

Books Received

Urology: A View Through The Retrospectroscope. By Dr John R. Herman. Pp. 196 with illustrations. Harper and Row. 1973. $7.95.

Management of Incontinence in the Home. P. Dobson. The Disabled Living Foundation, London, 1974 £1·20.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The list of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal*, *i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

Congenital Anomalies. Congenital abnormalities of the upper urinary tract. (C. S. Hoyt.) *Minn. Med.* 1973, **56**, 619.

Congenital abnormalities of upper urinary tract. (M. K. Ghosh *et al.*) *Minn. Med.* 1973, **56**, 637.

Beitrag zur Klinik und Therapie der uberzähligen Niere (Symptomatology and therapy of the supernumerary kidney. (S. Gödde.) *Urol. Int.* 1974, **29**, 56.

Lesions of the aortic junction associated with a horse-shoe kidney. (R. Kieny *et al.*) *J. Med. Strasbourg*, 1973, **4**, 867.

Observations on renal ectopia and fusion in children. (P. P. Kelalis *et al.*) *J. Urol.* 1973, **110**, 588.

Aberrant renal lobule: an anatomic variant in the differential diagnosis of intrarenal mass lesions. (S. A. Stuppler *et al.*) *Southern Med. J.* 1973, **66**, 1313.

Diffuse unilateral segmental renal hypoplasia with ureteral atresia, responsible for high blood pressure in childhood. Recovery after nephrectomy. (J. L. Andre *et al.*) *Arch. Franc. Pediat.* 1973, **30**, 831.

Trauma. Traumatic reno-caval arterio-venous fistula and duodenopancreatic injuries. Surgical care. (A. Wurtz *et al.*) *Chirurgie*, 1973, **99**, 489.

Late complications of closed trauma of the kidney. (J. Dormieux *et al.*) *J. Urol. Nephrol.* 1973, **79**, 486.

Bilateral traumatic renal artery thrombosis. (L. B. Ready *et al.*) *Canad. Med. Ass. J.* 1973, **109**, 885.

Traumatic diaphragmatic hernia of kidney with hypertension. (M. Ribet *et al.*) *Nouv. Presse Med.* 1973, **2**, 2750.

A little conscientious neglect seldom hurts a hurt kidney but lower tract trauma is a surgical emergency. (J. M. Pierce.) *Emergen. Med.* 1973, **5**, 89.

Renal trauma: West Virginia University Hospital analysis of 48 cases (1967-1972). (S. A. Stuppler.) *W. Virginia Med. J.* 1973, **69**, 309.

Renal tubular dysfunction following vascular accidents of the kidneys in the new born period. (H. Stark *et al.*) *J. Pediat.* 1973, **83**, 933.

Spontaneous extravasation of urine from renal pelvis and ureter. (E. W. Ramsey *et al.*) *J. Urol.* 1973, **110**, 507.

Fistula. Reno-alimentary fistula: unusual urological problem. (N. K. Bissada *et al.*) *J. Urol.* 1973, **110**, 273.

Infections. Common enterobacterial antigen in human chronic pyelonephritis and interstitial nephritis. (M. M. Schwartz and R. S. Cotram.) *New Eng. J. Med.* 1973, **289**, 830.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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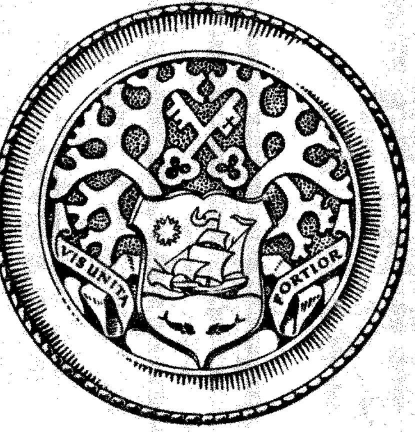

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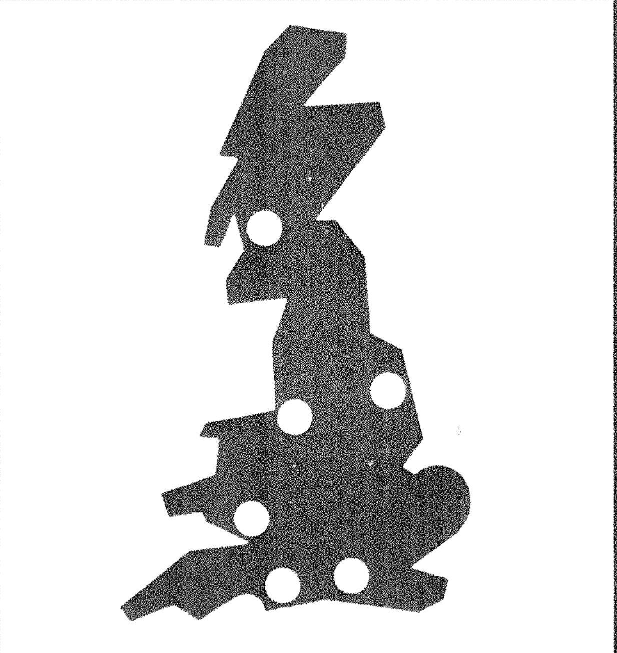
SEPTRIN TACTICS

they've taken the country



SEPTRIN* was rated top in a major British survey of urinary pathogen sensitivities.¹ Six clinical bacteriology laboratories—in Glasgow, Liverpool, Hull, Cardiff, Guildford and Salisbury—tested widely used antibacterials against a total of [illegible] urinary isolates (all species). The results showed that SEPTRIN outscored all other oral preparations. This survey complements clinical findings reported elsewhere of the superiority of SEPTRIN over ampicillin in urinary infections.[illegible]

[illegible]

Percentage sensitivity of isolates

	In-patients	Out-patients
SEPTRIN	[illegible]	[illegible]
Nitrofurantoin	[illegible]	[illegible]
Nalidixic acid	[illegible]	[illegible]
Ampicillin	[illegible]	[illegible]
Sulphonamides	[illegible]	[illegible]
Tetracycline	[illegible]	[illegible]

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Please indicate name and address to which requests for reprints should be made.

Format and content of papers

The text of articles submitted for publication should be typewritten in double-spacing on paper sheet size 22 × 32 cm (A4). There should be a minimum margin of 3 cm all round. The pages should be numbered.

Reports on clinical or laboratory investigation should as far as possible be organised into the following main sections: (1) Introduction, (2) Objective(s), (3) Patients or Materials, (4) Procedures or Methods, (5) Findings or Results, (6) Discussion and (7) Conclusions with (8) a Summary at the end.

Nephrology. Papers on disorders of renal function of interest to the urological surgeon are welcome.

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In all full papers the literature should be summarised as concisely as is consistent with establishing the necessary basis for new material. Discussions and Conclusions should be strictly limited to the results presented. Recapitulation from previous sections should be avoided whenever possible. Summaries should be composed of very brief statements about each of the main sections.

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continued on page v

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continued on page vii

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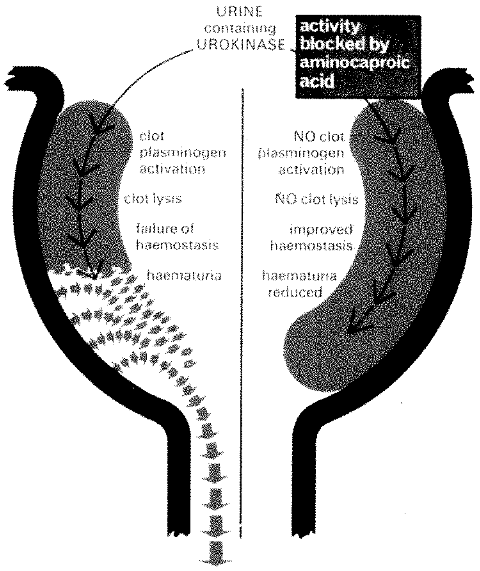
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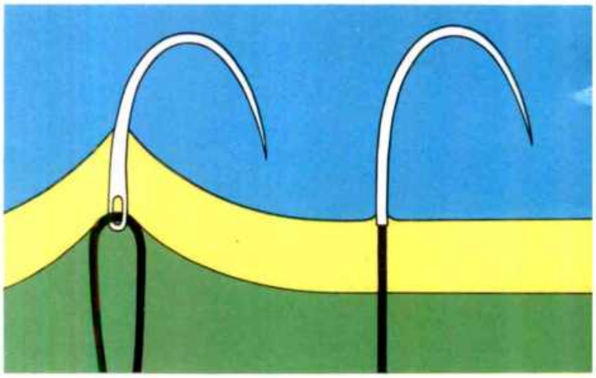

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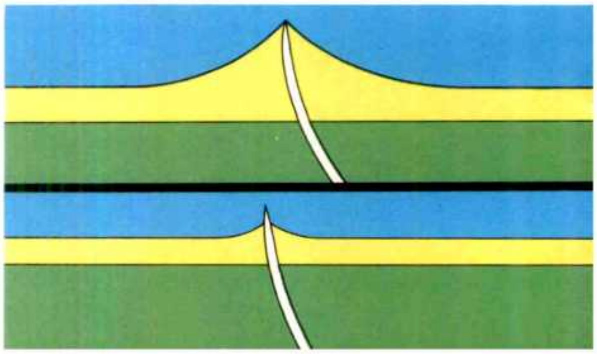

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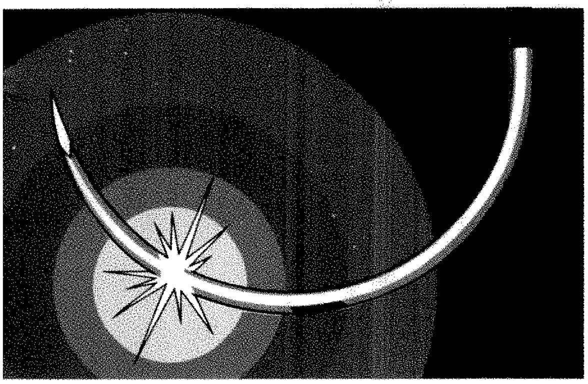

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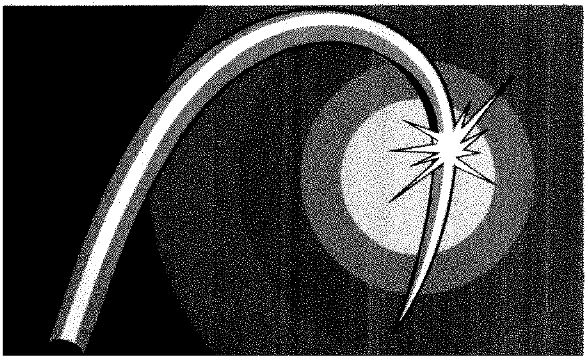

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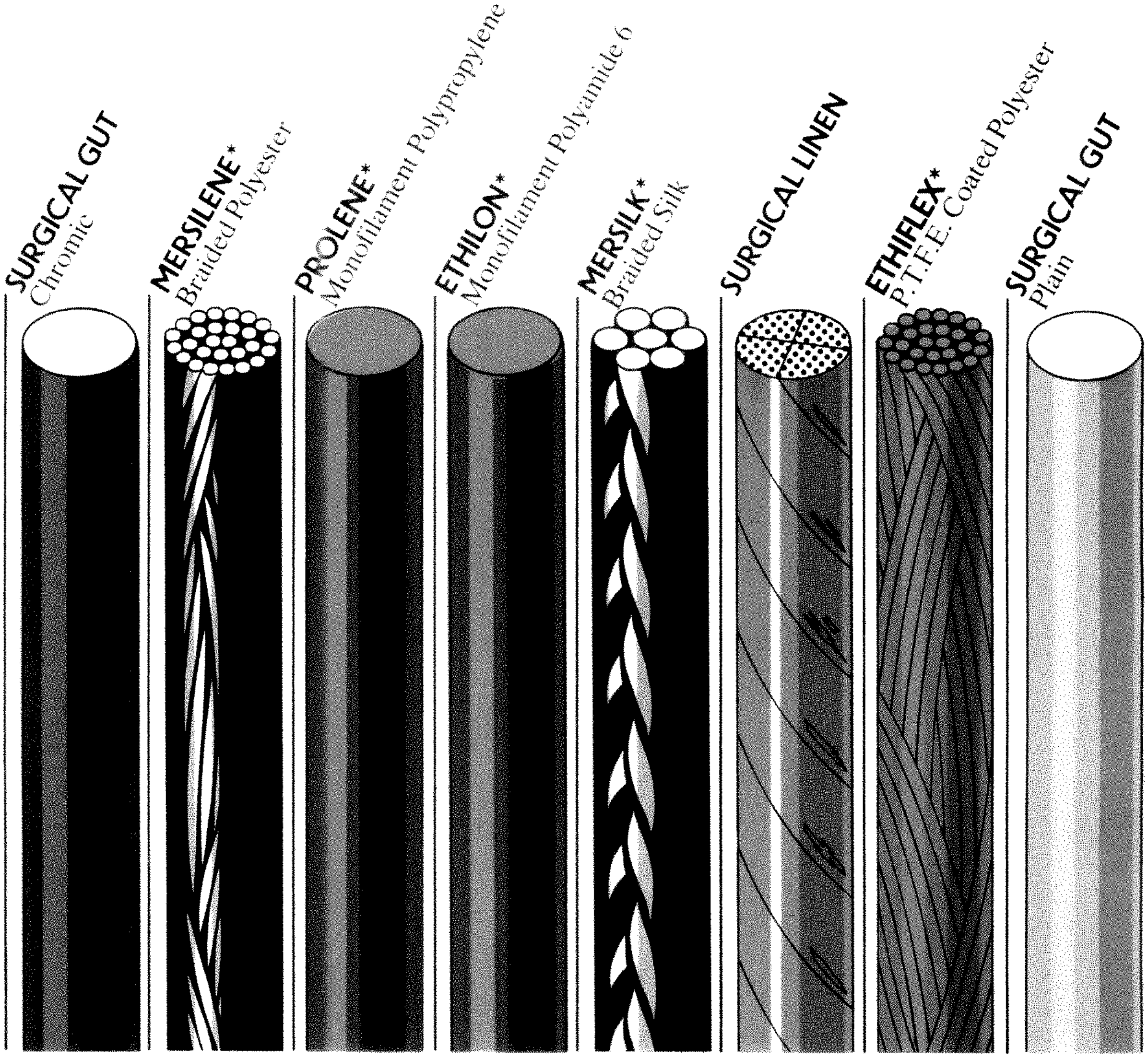

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Studies in depth

Amoxil compared with ampicillin

When Amoxil was first introduced to the Medical Profession in May 1972 it was hailed as the successor to ampicillin. Since then research teams and clinical trial workers all over the world have reported that Amoxil is superior to ampicillin. Some of their reports have been in areas which were anticipated, but others have confirmed important superiorities which could not be predicted. These reports are obviously of considerable interest to the discerning clinician, and inevitably there have been many requests for a compendium of the available work. This is now available and will be sent upon request to interested clinicians. Brief summaries of the main areas considered in the compendium are given below.

More effective than ampicillin

There is evidence that Amoxil is more effective than ampicillin and this is particularly well illustrated in respiratory infections. Indeed, some reports have confirmed that Amoxil can succeed where ampicillin has failed[1,2,3]

Absorption unaffected by food

Early reports confirmed that Amoxil is twice as well absorbed as ampicillin, giving a peak serum concentration of 5.3 μg/ml[4] as opposed to ampicillin's 2.3 μg/ml[5]. Further work has shown that if both drugs are taken in the non-fasting state the overall absorption of Amoxil over the following 6 hour period is not significantly reduced, whereas that of ampicillin is reduced by nearly a third.

Amoxil's absorption characteristics mean that it is taken t.d.s. as opposed to ampicillin's q.d.s., and that the patient need not remember to take every dose in the fasting state.

Superior penetration

Studies at the Brompton Hospital[6] have shown that whereas ampicillin penetrates well into purulent sputum it penetrates very poorly into mucoid sputum. These workers have shown that Amoxil penetrates equally well into both purulent and mucoid sputum, and suggest that this may have far-reaching consequences in the treatment of respiratory infections.

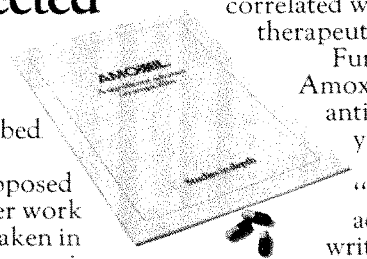
Better tolerated

Although ampicillin is generally well tolerated, rashes and diarrhoea can be an irritating nuisance. A review of published literature indicates that Amoxil produces substantially less rash and diarrhoea than ampicillin.

Greater potency

An ingenious series of experimental infections in mice has demonstrated that Amoxil exerts "... a more rapid bactericidal effect than ampicillin and this could be correlated with the difference in therapeutic effect."[7]

Further studies comparing Amoxil in depth with other leading antibiotics are in preparation. If you would like to receive a copy of the booklet "Amoxil – a significant advance on ampicillin" please write to the Freepost address given below. No stamp is required.



AMOXIL

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References: (1) Brit. J. Dis. Chest., (1972), 66, 185. (2) S.A. med. J., (1973), 47, 717. (3) Chemotherapy, (1973), 18, (Suppl.), 19. (4) Brit. med. J., (1972), 3, 13. (5) Antimicrobial Agents and Chemotherapy (1970), 438. (6) To be published (7) Antimicrobial Agents and Chemotherapy, (1970), 416.

Full information on Amoxil (regd.), amoxycillin, is available from:

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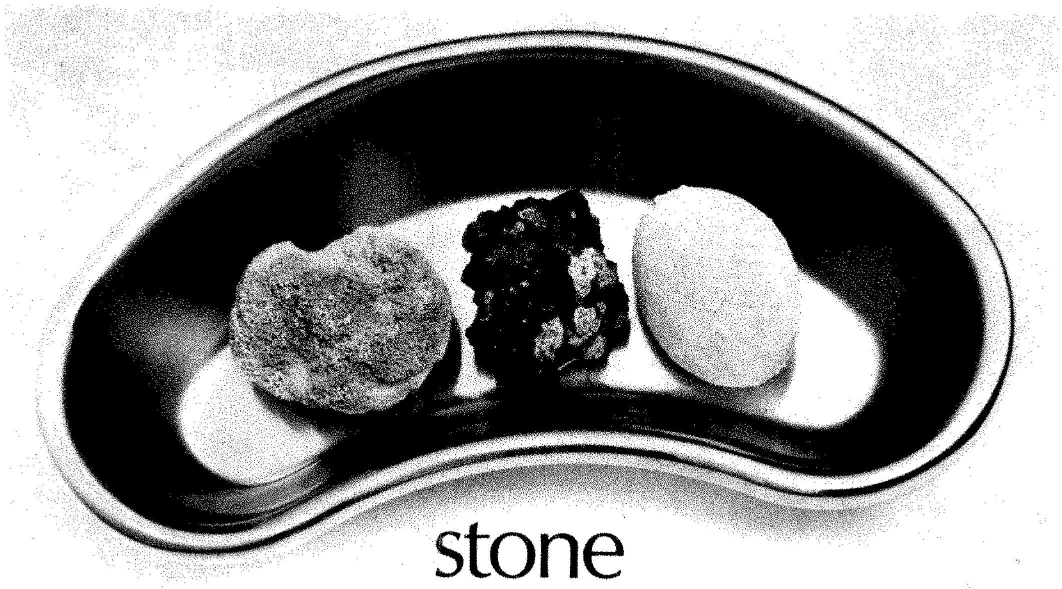

stone stopping comments no. 3

Whatman Sodium Cellulose Phosphate has been shown to be particularly useful in long-term therapy and as a prophylaxis against recurrent calcium stones.[1,2,3]

A recent American trial[4] confirms the therapeutic and prophylactic value of cellulose phosphate in hypercalciuria and nephrolithiasis. Sixteen patients with recurrent renal stones were given a low-calcium diet with 5g cellulose phosphate b.d. or t.d.s. Long-term (0.3—4 years) assessments of various urine and serum measurements were made every 1—6 months prior to the start of therapy. Treatment ranged from 1½—4⅔ years.

"Clinically, renal-stone formation virtually ceased. The treatment was well tolerated, and no serious side-effects have been observed."

"Characteristic responses to treatment... were as follows: a decrease in the urinary excretion of calcium, usually to within the normal range; a reduction in the urinary state of saturation with respect to brushite...; and a virtual freedom from renal colic and cessation of passage of renal stones or of formation of new stones."

The authors also observed that the effects quoted above persisted for as long as 4.8 years, and there was no indication of escape from drug therapy.

Commenting on cellulose phosphate vis à vis orthophosphate, the authors found the former to be preferable in absorptive hypercalciuria and nephrolithiasis:

"...orthophosphate causes a more marked phosphaturia and a smaller reduction in urinary calcium... Orthophosphate renders urine more supersaturated with respect to brushite... but it inhibits the propensity for the spontaneous nucleation of brushite.... Finally, although orthophosphate has been shown to prevent stone formation,... it has been found to cause extraskeletal calcification..."

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References

1. Amer J Med. (1971) **50**, 67-76.
2. J Clin Pharmacol. (1973) **13**, 15-27.
3. Brit J Urol. (1973) **45**, 136-143.
4. New Engl J Med. (1974) **290**, (4), 175-180.

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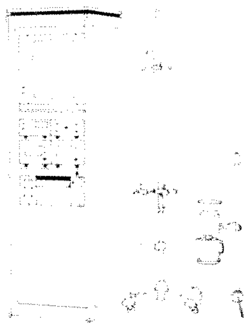

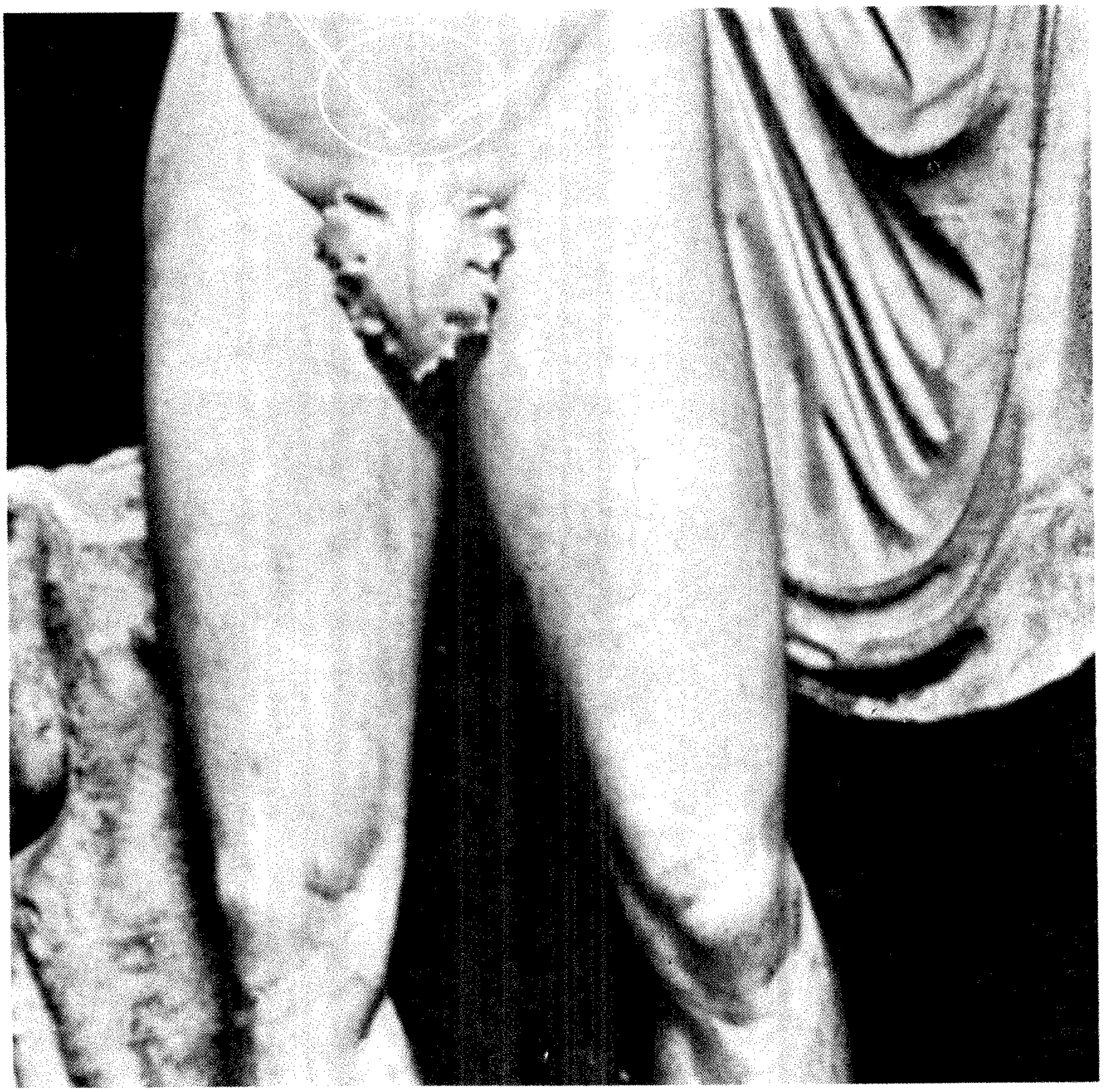

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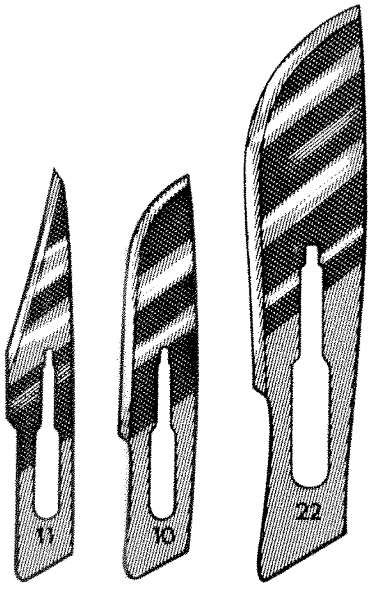

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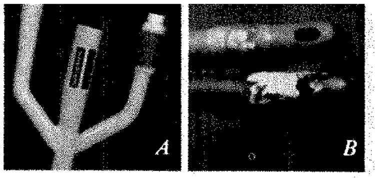

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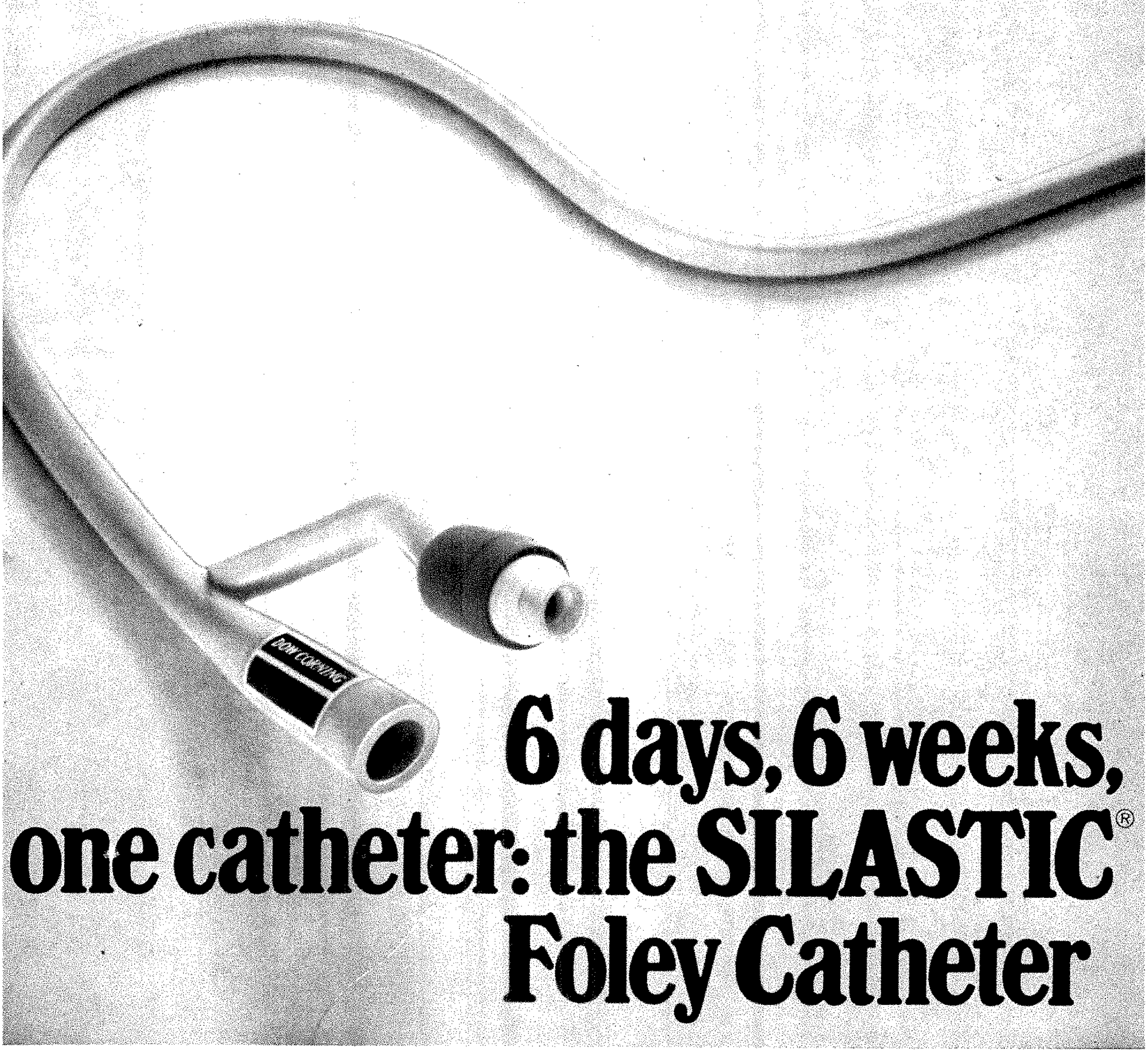

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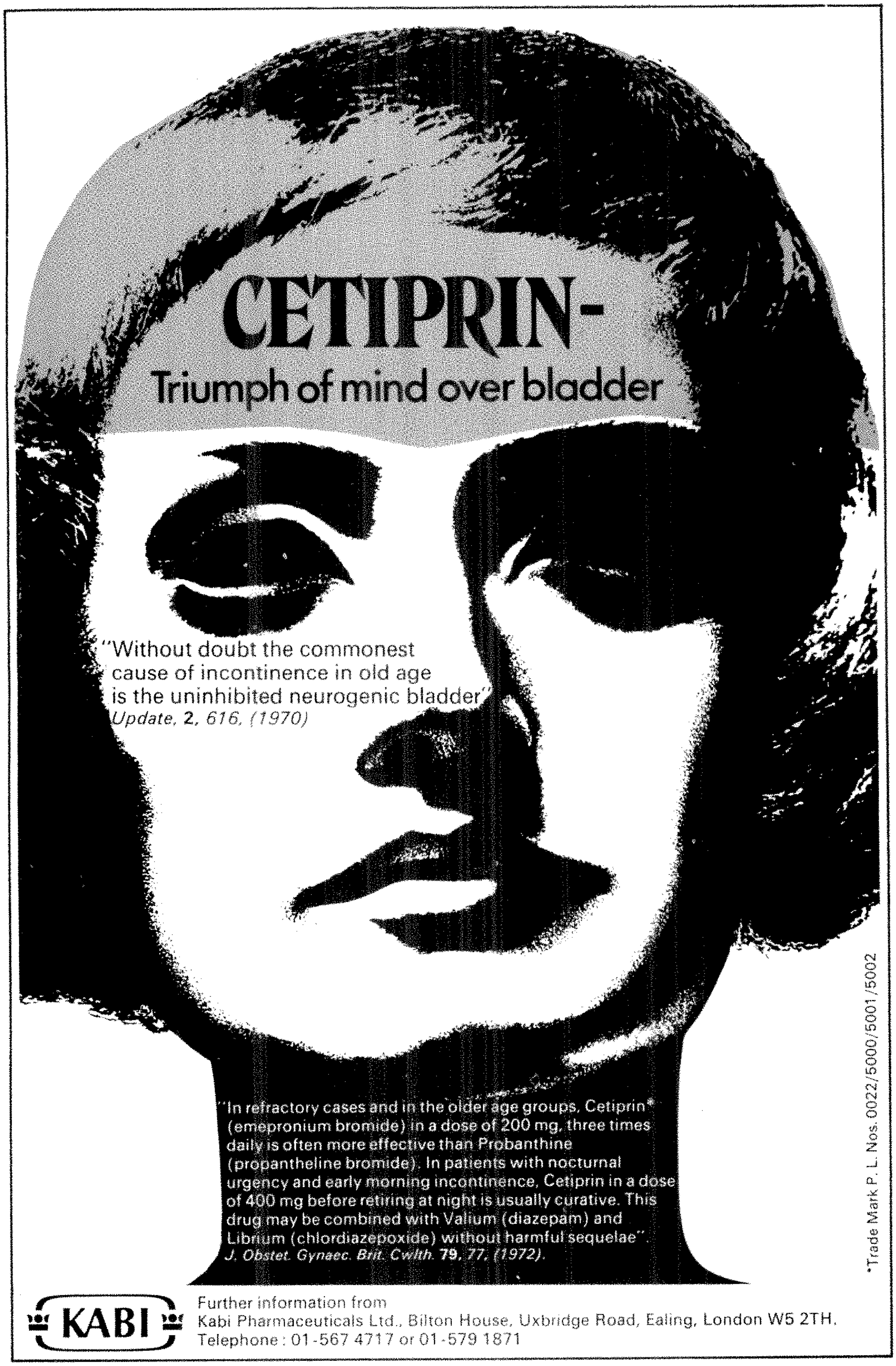

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Genetic Aspects of Hydronephrosis Associated with Renal Agenesis

RONALD FINN and J. A. CARRUTHERS

Liverpool Regional Urological Centre, Sefton General Hospital, Liverpool and the Nuffield Unit of Medical Genetics, University of Liverpool

The aetiology of hydronephrosis with pelvi-ureteric obstruction is, in some cases, obvious, for example when a stricture or lower-pole renal vessel is found. However, in a large number of cases the aetiology is obscure. The hereditary aspects of this condition have received little attention and as recently as 1958 a review of the genetic aspects of urology did not mention hydronephrosis (Burkland, 1958). A review of the literature has revealed only 4 families with hydronephrosis and the purpose of this article is to report a further 2 families and to discuss the pathogenesis and genetic aspects of hereditary hydronephrosis.

Case Histories

Family A (Fig. 1)

Case 1A. This woman, the mother of the presenting patient, was well and the I.V.P. was normal (Fig. 2).

Case 2A. The father, aged 63, was well and asymptomatic; however the I.V.P. and tomograms revealed an absent right kidney and mild pelvi-ureteric obstruction on the left (Fig. 3). Cystoscopy was not considered justified.

Case 3A. This man was the presenting patient for this family. At the age of 19 years he presented with haematuria, was found to have bilateral hydronephrosis with pelvi-ureteric obstruction and had bilateral plastic repair operations. He had no other congenital malformations and was otherwise well. A recent I.V.P. (Fig. 4) reveals a hydronephrosis on the right side with no function on the left.

Case 4A. The patient's sister was well and had a normal I.V.P. (Fig. 5). It is noted that the renal pelves have a globular shape.

Case 5A. The remaining sibling was also asymptomatic, but the I.V.P. showed mild, but definite, bilateral pelvi-ureteric obstruction (Fig. 6).

Family B (Fig. 7)

Case 1B. This woman was discovered to have a right hydronephrosis with pelvi-ureteric obstruction at the age of 43 years, and this was treated with a plastic repair operation. She died of an atrial sarcoma, aged 67.

Case 2B. The husband of Case 1B died of "bronchitis" aged 67 and no I.V.P. is available.

Case 4B. This man was discovered at the age of 23 years to have severe left pelvi-ureteric obstruction. He was treated with a left plastic repair operation.

Case 5B. This man has mild essential hypertension with a normal I.V.P.

Case 8B. This woman is known to have had 1 renal calculus, but here I.V.P. shows no pelvi-ureteric obstruction.

Case 9B. This woman presented with intermittent left loin pain which she had had for some years. The I.V.P. showed mild left pelvi-ureteric obstruction (Fig. 8).

Case 3B, 6B and **7B** were not available for study, but were apparently well.

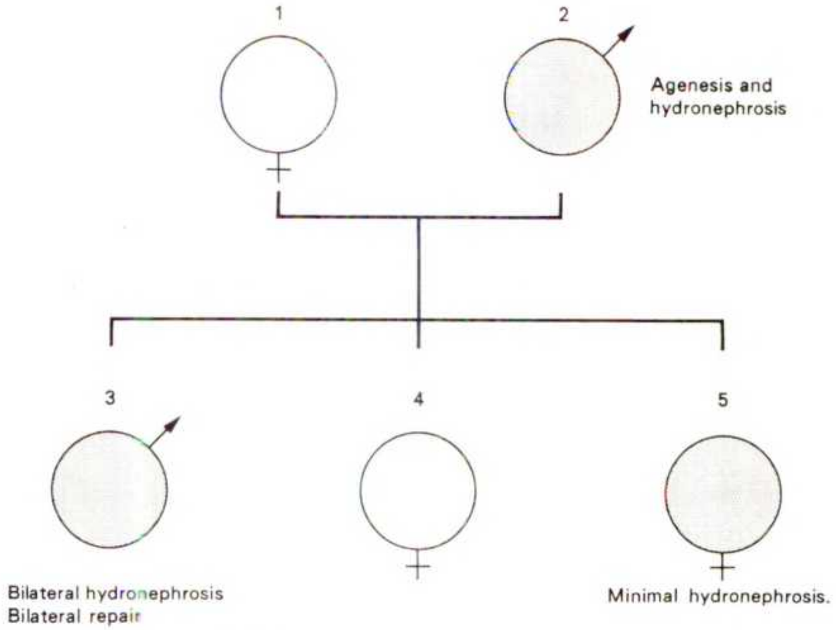

Fig. 1. Family tree of Family A.

Discussion

There have been 4 families with pelvi-ureteric obstruction previously reported. The first of these (Cannon, 1954) had 5 cases in 3 generations, all of whom were male. Two infants required removal of grossly hydronephrotic kidneys, one in the neonatal period and the other at 11 months. The 3 other members had mild unilateral hydronephrosis and pelvi-ureteric obstruction, not requiring surgery. Orr (1961) described a family, 5 of whose members had hydronephrosis of varying degree, 1 of whom had a solitary hydronephrotic kidney and 3 of whom had bilateral hydronephrosis. Jewell and Buchert (1962) reported a family with 4 cases of pelvi-ureteric obstruction in 3 generations, all of whom had unilateral hydronephrosis. Finally, Campbell (1970) mentions a family where mother, son and daughter all had left pelvi-ureteric obstruction.

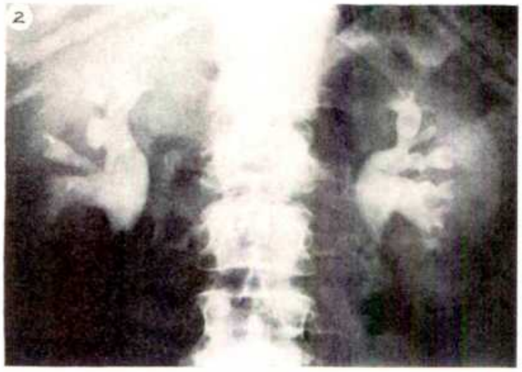

Fig. 2. Normal I.V.P. of Case 1A.

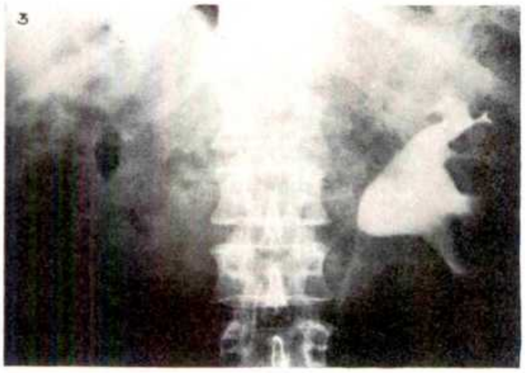

Fig. 3. I.V.P. of Case 2A showing mild left pelvi-ureteric obstruction with an absent right kidney.

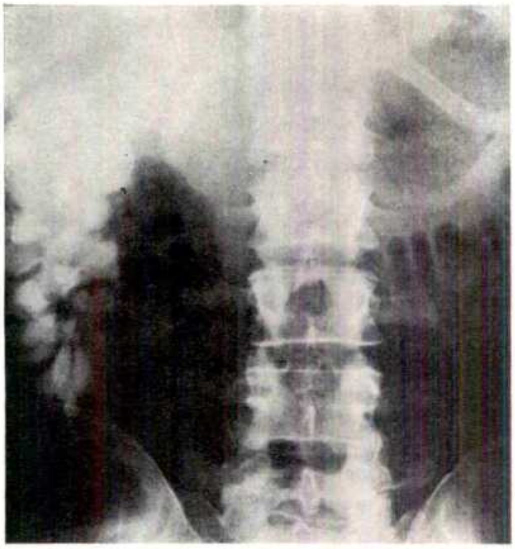

Fig. 4. I.V.P. of Case 3A showing right-side hydronephrosis and absent function on the left.

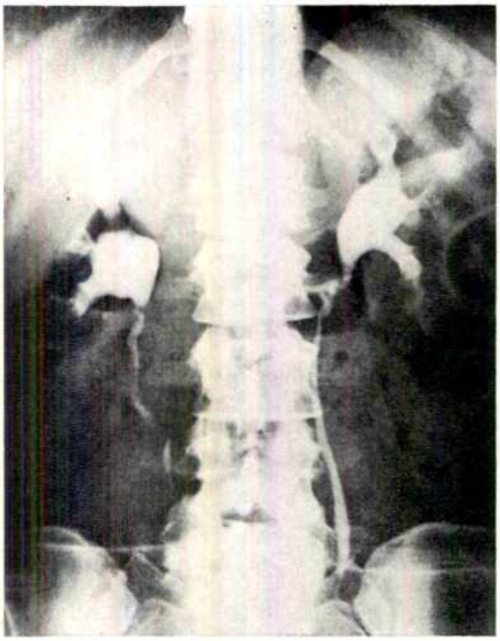

Fig. 5. Normal I.V.P. of Case 4A.

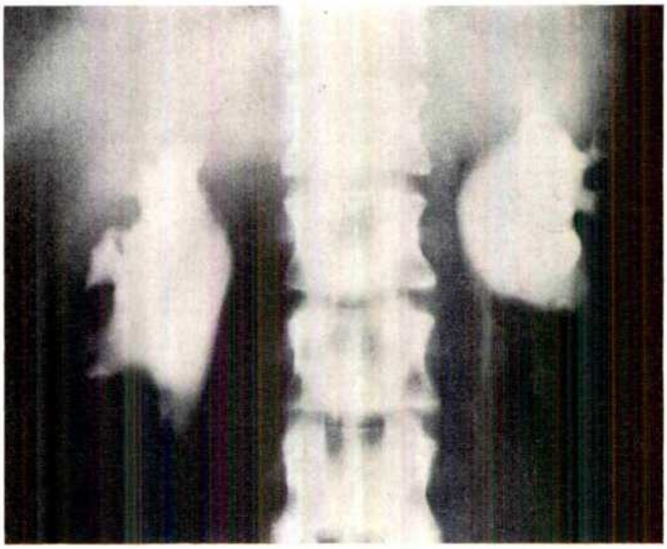

Fig. 6. I.V.P. of Case 5A showing bilateral mild hydronephrosis.

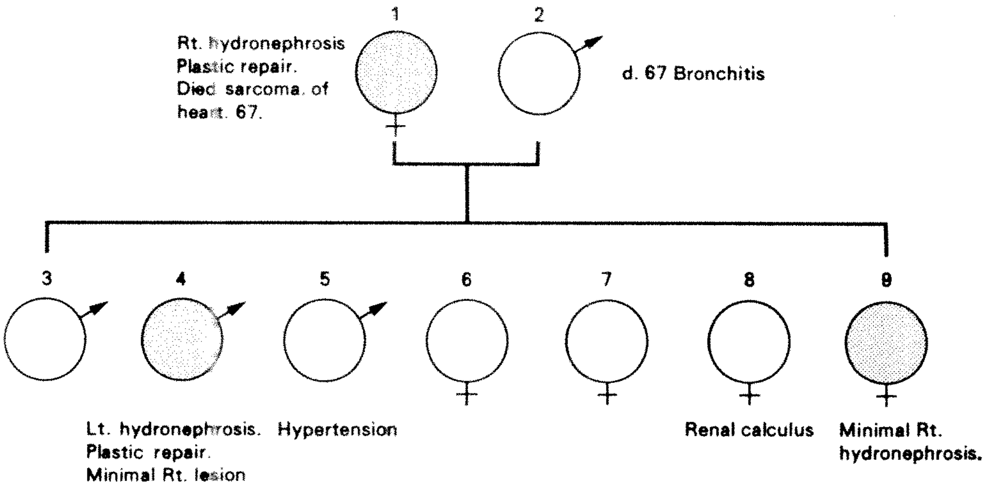

Fig. 7. Family tree of Family B.

Work on animals has contributed greatly to our understanding of the inheritance and pathogenesis of hereditary hydronephrosis. In mice a number of genes are known to affect the incidence of hydronephrosis, the gene for short ear (*se*) being the most extensively studied (Wallace and Spickett, 1967). It is interesting that, apart from 1 stock in which hydronephrosis is associated with diabetes insipidus, the other region most consistently affected by these genes is the musculoskeletal system, with skeletal, cartilaginous and neuro-muscular defects. The short ear gene produces, in homozygotes (*sese*), shortness of ear and other skeletal anomalies, including bifurcation or reduction of the xiphoid processes of the sternum, reduction in the numbers of pairs of ribs and reduction in the size of parts of several small bones in various areas of the skeleton. Two additional effects are seen in both homozygotes (*sese*) and heterozygotes (*se*+), namely "kinky-tail", which appears to be due to a neuro-muscular defect, and hydronephrosis, which occurs in 28% of homozygotes and 16% of heterozygotes. Hilson's description (Hilson, 1957) of congenital urological abnormalities, including hydronephrosis, in patients with congenitally deformed ears and the familial nature of this trait suggests that parallels may legitimately be drawn from work on mice with the short ear gene to the situation in man.

Wallace and Spickett (1967) showed that *se* heterozygotic mice are less often hydronephrotic than *se* homozygotes, and that hydronephrosis in the heterozygote is usually associated with abnormal vasculature of the ureter. The homozygotes, on the other hand, tend to be hydronephrotic whether the vascular abnormality is present or not. The vascular abnormality consists

Table I

	Cannon	Jewell and Buchert	Orr	Campbell	Present Series	Total
Male	5	2	2	1	3	13
Female	0	3	3	2	3	11
Left	4	4	1	3	1	13
Right	1	1	1	0	2	5
Both	0	0	3	0	3	6

of the blood supply of the upper ureter and pelvi-ureteric junction coming from below, rather than from the renal vessels as is usually the case. The data indicates that the *se* gene is recessive for the musculo-skeletal effects, but dominant with variable penetrance for hydronephrosis. The degree of penetrance depends on certain secondary factors, being greater in homozygotes and in individuals with the ureteric vessel abnormality.

Analysis of the available human data clearly shows that the gene for hydronephrosis is also an autosomal dominant. It is also clear that the penetrance is variable, as indicated, for example, by our Cases 3A and 5A. The animal studies have demonstrated that hydronephrosis is commoner in the male. Analysis of the limited human material does not bear this out (Table I), but there is a suggestion that the condition may be more severe in the male. Hilson (1957) has shown that genito-urinary abnormalities associated with malformed ears are more common on the left and it is therefore of interest that the limited data from the families with hydronephrosis also show this tendency (Table I).

The mouse experiments leave little doubt that constriction due to lower-pole renal vessels is not the primary cause of hereditary hydronephrosis because this lesion was not found in the affected animals. It is, therefore, likely that the primary abnormality is neuro-muscular and it is of interest that Murnaghan (1958) has shown that hydronephrosis in human patients is frequently secondary to failure of propagation of the waves of muscular contraction at the pelvi-ureteric junction. The presence of vascular abnormalities, such as those described in the mouse experiments, might exacerbate the condition and could convert a mild pelvi-ureteric obstruction into a clinically significant hydronephrosis.

It is apparent from our cases that there are many grades of this condition varying from a slightly globular renal pelvis to a severe obstructive hydronephrosis. One of our patients (Case 9B) presented with a long history of intermittent loin pain for which no cause could be found and had been considered to be neurotic. The I.V.P. (Fig. 8) showed a very mild degree of left pelvi-ureteric obstruction which had hitherto been accepted as being within normal limits. However, when taken in conjunction with the clinical picture and the family history, we have no doubt that this is the cause of her pain. Wallace and Spickett write that, in *se* mice with the vascular abnormality, "... there is interruption in the wave of muscular contraction (at the pelvi-ureteric junction) with incipient kink formation. . . . It is possible that this slight inco-ordination and incipient kinking leads to actual periodic occlusion in mildly hydronephrotic mice." We feel

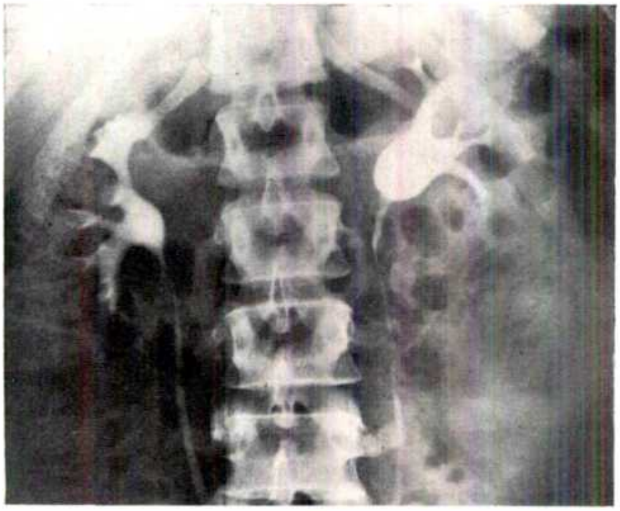

Fig. 8. I.V.P. of Case 9B showing mild left hydronephrosis.

than an analogous situation exists in man. Varying grades of clinical severity would include asymptomatic mild dilatation of the renal pelvis, intermittent obstruction causing attacks of pain as in Case 9B, or a predisposition to stasis possibly leading to infection or calculus formation. It is therefore possible that this mild form of the disease may be responsible for more pathology than has hitherto been realised.

Finally, we report the association, in one of our patients, of unilateral hydronephrosis with contralateral renal agenesis. This also occurred in one member of Orr's family and there was a further possible case in Jewell and Buchert's family. The available data would therefore indicate that this is a real association and renal agenesis may represent the most extreme form of the basic abnormality, which in less severe cases is manifested by pelvi-ureteric obstruction.

Summary

Two families with hereditary hydronephrosis are reported and a further 4 families form the literature reviewed. In these families the condition may be unilateral or bilateral, and if unilateral, is more common on the left side.

Hereditary pelvi-ureteric obstruction is due to an autosomal dominant gene with variable penetrance. Evidence from animal studies relating to the pathogenesis of pelvi-ureteric obstruction is discussed.

It is suggested that the mild form of the condition may have more clinical significance than has been previously realised. The association of renal agenesis and hereditary hydronephrosis is also noted.

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Requests for reprints to R. F.

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Autonomic Innervation of the Renal Calyx

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That the renal collecting system and ureter has a considerable nerve supply is not in doubt. Wharton (1932) and Mitchell (1936), in their painstaking dissections of the human foetus, have shown nerves to pass from the abdominal autonomic plexuses to the ureter. Also, the presence of an adventitial plexus of unmyelinated nerve fibres is agreed by most workers. Fibres from this plexus have been found to pass through the muscle layer and into the submucosa, but only sparse anatomical evidence of terminal nerve areas lying adjacent to actual smooth muscle cells has been presented (Duarte-Escalante, Labay and Boyarsky, 1969; Notley, 1970; Gosling and Waas, 1971). Some of these nerves are probably efferent to vascular smooth muscle, and it is possible that the remaining fibres are solely afferent in function—we are all aware of the ease with which pain can be elicited by distending the collecting system. However, alteration in the motor function of the ureter has been claimed to occur after experimental stimulation of the renal plexus, splanchnic and hypogastric nerves (Satani, 1919; Boyarsky, Labay and Glenn, 1968). Autonomic neurotransmitter substances have also been found by many workers to influence the basically autonomous activity of the system.

A firm knowledge of the part, if any, played by the autonomic nerves in control or modulation of motor activity in the collecting system and ureter would appear to be essential if we hope to gain further knowledge of the pathogenesis and perhaps treatment of dysfunctions such as idiopathic hydronephrosis, hydrocalycosis, mega-ureter and uretero-vesical reflux. With this in mind it was decided to investigate the renal collecting system and ureter by means of an isolated tissue technique. The aim was twofold: firstly to identify the pattern of autonomic receptors present in calyx, pelvis and ureter, and secondly to attempt to relate these receptors to the nerve fibres seen anatomically to lie in their vicinity. The presence of autonomic receptor sites in smooth muscle does not, as has often been thought, imply that there must necessarily be a concomitant nerve supply. For example, the smooth muscle cells of the chick amnion are a "veritable Garden of Eden of receptors", yet the tissue is completely devoid of nerves. So far due to difficulty in obtaining sufficient numbers of suitable human material for study, the majority of the work has been carried out on animal tissue, and results presented here refer to the renal calyx of the pig.

Materials and Methods

1. Procedure

At a local abattoir, kidneys were obtained from 30-week-old male pigs within 15 minutes of the animals' death. They were immediately sectioned by introducing one blade of the dissecting scissors through the orifice in the few millimetres of attached ureter, and making a cut through the medial border of the kidney substance first to the upper pole and then to the lower. The kidney could then be opened like the leaves of a book to reveal the renal papillae projecting into each calyx. A strip of calyceal tissue approximately 1 cm by 3 to 4 mm was then carefully dissected from around the base of a papilla in a circumferential manner. Specimens so obtained were placed immediately in Krebs solution at approximately 37°C and transported to the laboratory in a portable apparatus allowing aeration of the nutrient medium with a 96% O_2 to 4% CO_2 mixture.

Using 6–0 atraumatic Mersilk sutures, the tissue was suspended in a 20 ml jacketed organ bath containing Krebs solution at $38 \pm 0{\cdot}5$°C, and well aerated via a glass scinter with a 95% O_2 to 5% CO_2 mixture (Fig. 1). The bath could be repeatedly refilled with an exactly similar fluid contained in an 100 ml preheating column. One end of the strip of calyx was firmly anchored to the base of the bath, while the other was attached to a force displacement transducer, which in turn gave a permanent tracing of changes in tension on a potentiometric recorder.

Approximately 300 mg resting tension was applied to the specimen, and after a period of 15 minutes to allow for equilibrium, drugs were added to the bath usually according to a 6-minute cycle, *i.e.* 2 minutes control period, 2 minutes drug contact, and 2 minutes wash. Field stimulation was achieved by the use of 2 platinum electrodes of 1 mm diameter. These were arranged on either side of the tissue so that the distance separating each electrode was 8 mm. By this means the tissue could be stimulated transmurally with electrical square-wave pulses of varying frequency, intensity and duration.

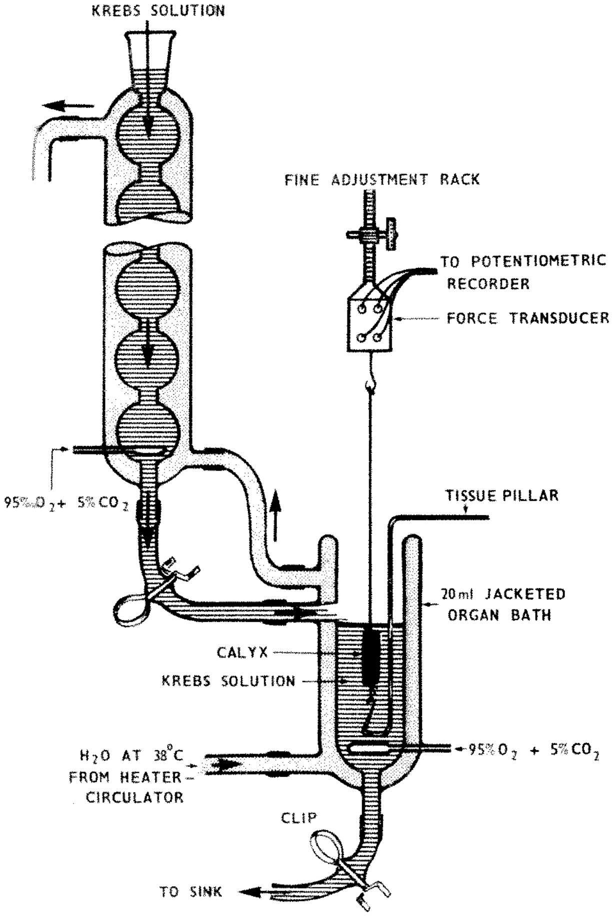

Fig. 1. Diagrammatic representation of apparatus used.

2. Drugs

The following drugs were used in this investigation: (−)—phenylephrine hydrochloride (Koch Light); (−)—noradrenaline and (−)—adrenaline as acid tartrate (Koch Light); (DL)—isoprenaline sulphate (Sigma); acetylcholine chloride (Koch Light); atropine sulphate monohydrate (Koch Light); phentolamine mesylate (Ciba); propanolol (I.C.I.); cocaine hydrochloride (Boots); tetrodotoxin (Sigma); tyramine hydrochloride (Sigma). A stock solution of 10^{-2} gm/ml was prepared every 2 weeks and stored at 4°C, dilutions for each experiment being made daily as required. Drug concentrations in the text refer to amounts of the salt present in the organ bath fluid.

3. Krebs Solution

The following were dissolved and the final volume adjusted to 1 litre using distilled water: KCL, 0·35 g; $MgSO_4$, 0·29 g; KH_2PO_4, 0·16 g; $CaCl_2$, 0·37 g; NaCl, 6·9 g; NaH CO_3, 2·1 g; glucose, 2 g.

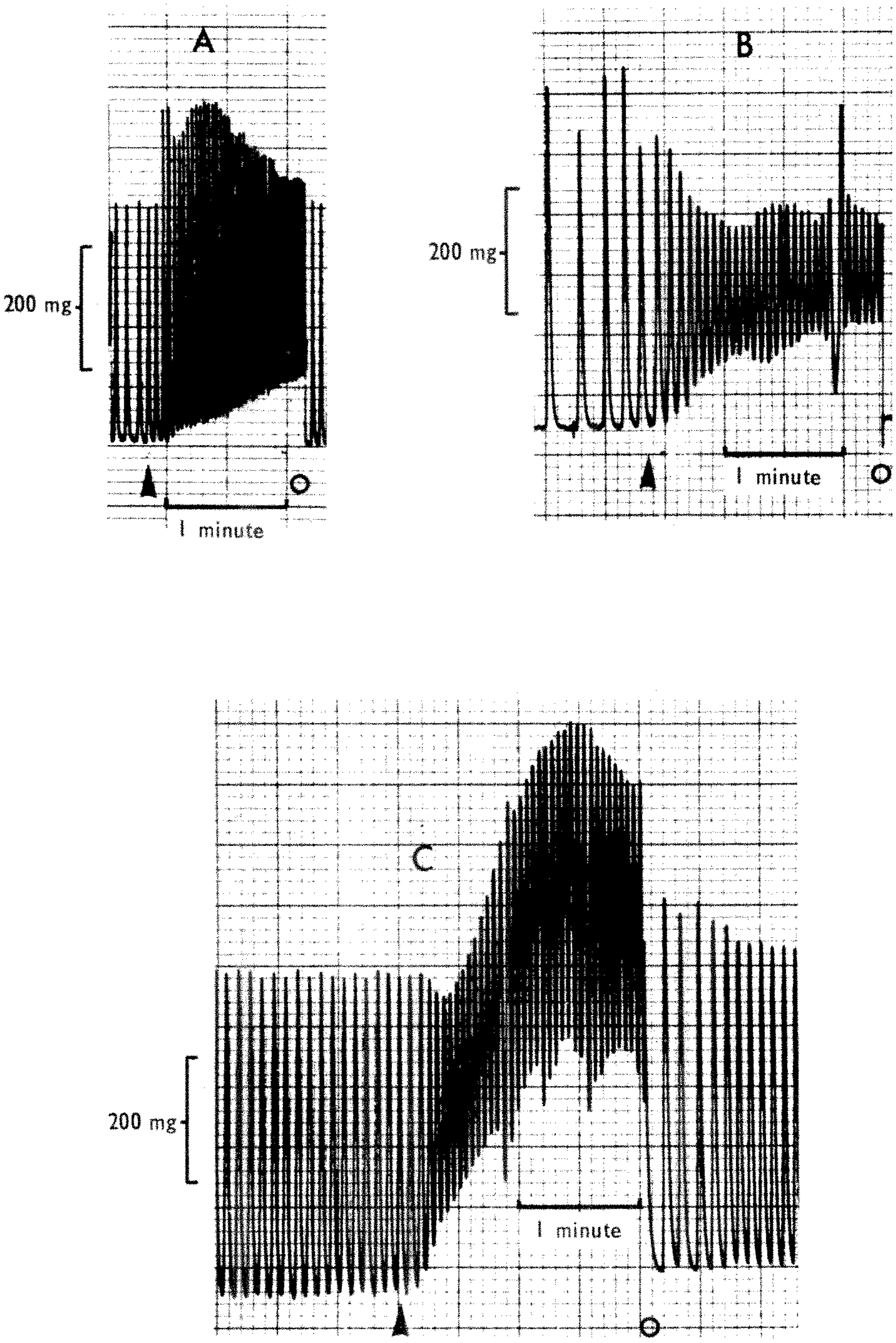

Fig. 2. Recordings from 3 separate preparations of calyx to show effects of similar concentrations (1 μg) of adrenaline (C), noradrenaline (B), and phenylephrine (A). Each drug was added at ▲ and the tissue washed with Krebs solution at ○.

Results

Most preparations immediately exhibited regular, rhythmical changes in tension in the range of 0·2 to 1·0 g and at a rate of 5 to 8 per minute. Those which did not show this regularity of contraction were excluded from the study. After initial interference with the fresh tissue, either by drug addition or by electrical stimulation, some preparations increased their rate of spontaneous activity and remained at this higher level for the duration of the experiment.

Phenylephrine, noradrenaline and adrenaline each caused an increase in resting tension together with an increase in frequency of spontaneous contraction (Fig. 2 A, B and C). Changes in amplitude were variable. Isoprenaline resulted in a decrease in resting tension, a decrease in rate of tension changes, and a slight increase in amplitude (Fig. 3). The effects were dose-dependent, and logarithmic concentration-effect curves were plotted for each drug utilising changes in tension as the measurable effect for the former three drugs, and frequency of spontaneous contractions for the latter. The measurement of changes in resting tension was found to give the most reproducible results for drugs possessing a stimulatory action. However, in the case of the inhibitory response effected by isoprenaline, this parameter could not be used because the tissue was capable of only a limited small decrease in resting tension owing to the nature of the experimental technique used. With this drug therefore the effect was measured as a decrease in the frequency of spontaneous contractions, and the results again found to be reproducible. Adrenaline and noradrenaline gave equal maximum responses, and effects of these two drugs were expressed as a percentage of this maximum. Similarly the effects of isoprenaline were expressed as a percentage of the maximum response obtained with this drug. Representative 'curves' for each drug are shown in Figures 4 and 5. There was considerable variation in the sensitivity of different preparations to noradrenaline and adrenaline, and the results of 6 experiments with each drug were pooled to plot the graph in Figure 6. Only values between 10% and 90% were included in order that the method of "least squares" could be used to find the best fitting straight line for each set of points. Phenylephrine was found to be capable of eliciting only 65% of the maximum response seen with noradrenaline and adrenaline, even at very high doses, and possible explanations of this are discussed later.

Phentolamine, an α-adrenergic blocking agent, was found to antagonise the actions of adrenaline, noradrenaline and phenylephrine. Figure 7 shows the effect of equal concentrations of adrenaline in the presence of increasing concentrations of phentolamine. This behaviour of the tissue to noradrenaline, adrenaline and phentolamine was further pursued in an attempt to characterise the receptors for these drugs in a quantitative manner by the pA_x method. Before presenting the results, the concept of pA_x will be briefly summarised together with its method of determination.

pA Concept and method of determination

In order to assess drug antagonism quantitatively in a manner allowing comparison of results obtained by varying experimental techniques on different tissues, Clark and Raventós (1937) proposed to use as the measure of activity the concentration of antagonist necessary to neutralise the effect of a tenfold increase of active drug. This idea was modified slightly by Schild (1947) when he introduced the pA scale of measurement which is simply a more convenient form of expression. pA_x is defined as the negative logarithm to base 10 of the molar concentration of an antagonist drug which will reduce the effect of a multiple dose (x) of an active drug to that of a single dose. Thus, if the presence of a concentration of $10^{-7\cdot0}$ molar phentolamine in the organ bath fluid reduces the effect of 2 μg adrenaline to that produced in the absence of phentolamine by 1 μg adrenaline, then the pA_2 for phentolamine-adrenaline will be 7·0.

In the present study, pA_2 and pA_{10} values were calculated for noradrenaline and adrenaline by the following method. An approximately EC_{50}[1] dose (x) of the active drug is repeatedly given to the preparation until a constant response is obtained, again measuring changes in resting tension. The principle then consists of finding, by trial

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[1] That concentration of a drug required to effect a 50% of maximum response.

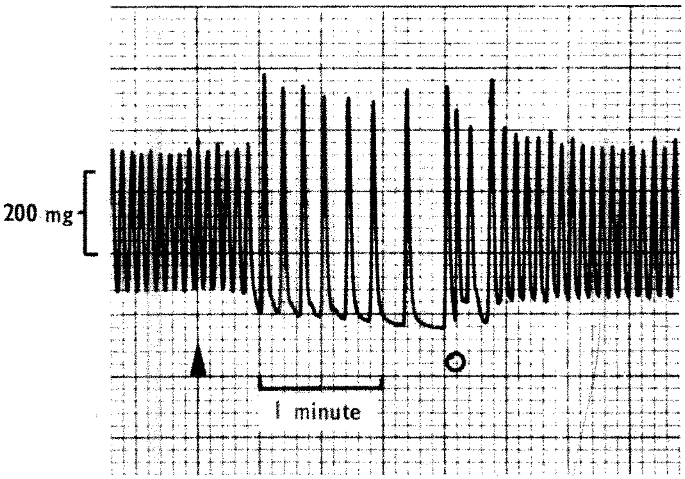

Fig. 3. Effect of 0·125 μg isoprenaline on spontaneous activity of isolated calyx. The drug was added at ▲ and the tissue washed with Krebs solution at ○, with rapid return of control contractions.

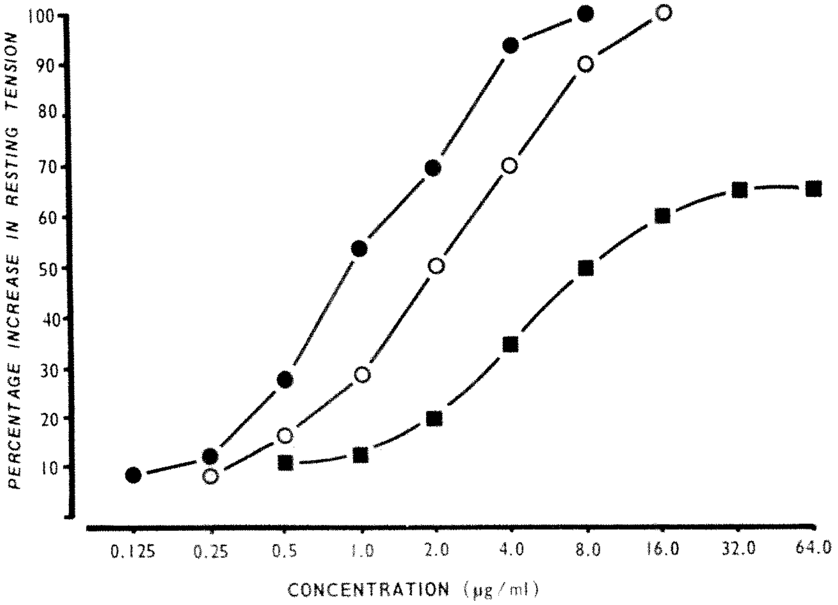

Fig. 4. Logarithmic concentration-effect curves for adrenaline (●), noradrenaline (○) and phenylephrine (■) on the isolated calyx.

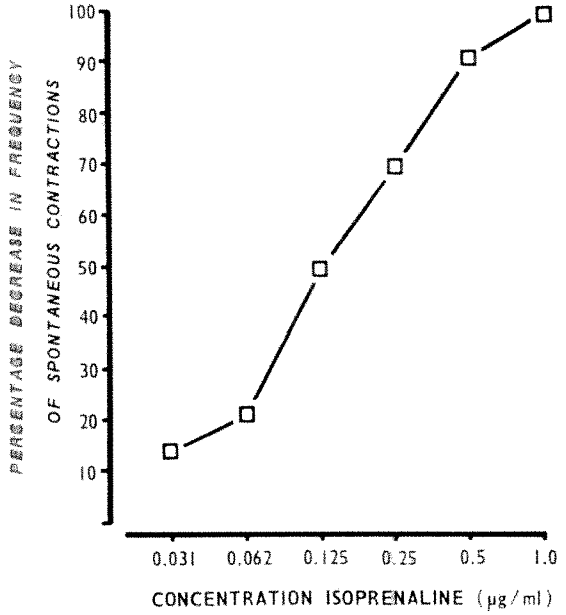

Fig. 5. Logarithmic concentration-effect curve for isoprenaline on isolated calyx. The effect is expressed as a percentage of the maximum obtainable with the drug, *e.g.* 1 μg effects a 100% response which implies complete cessation of spontaneous activity.

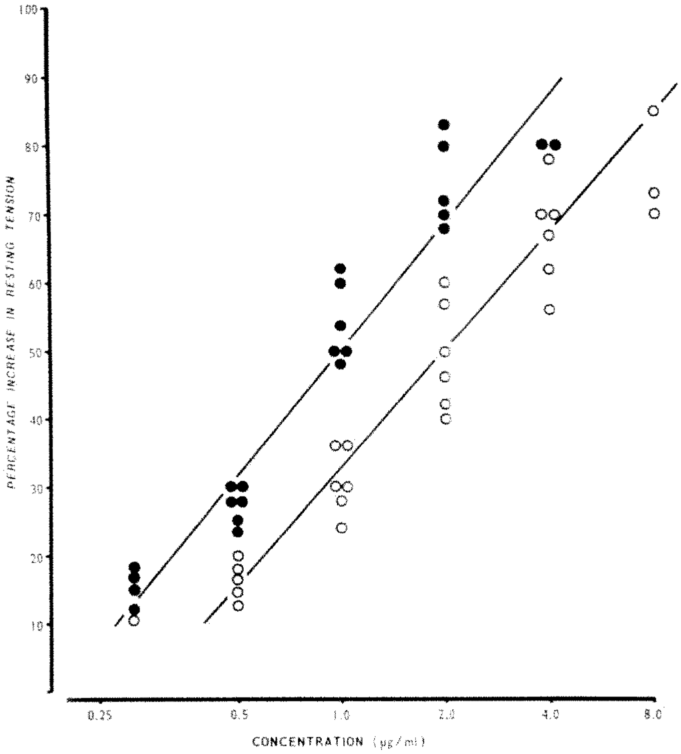

Fig. 6. Logarithmic concentration-effect lines for adrenaline (●) and noradrenaline (○) on isolated calyx. The results are of 6 experiments with each drug, excluding values above 90% and below 10%.

and error, a concentration of the antagonist drug such that it will reduce the effect of a $2x$ dose of the active drug to slightly less than would be expected in the absence of the antagonist. The concentration of antagonist is then increased, and the response of the same double dose noted as in Figure 7. This procedure is repeated until the response of the double dose is less than that of a single dose, and the relationship of agonist and antagonist plotted as in Figure 8. A straight line of negative slope results, from which the concentration corresponding to pA_2 is then computed by interpolation. An exactly similar method is used to calculate a pA_{10}, the double dose of agonist ($2x$) being replaced by a $10x$ dose (Fig. 8). The results are then converted to the molar form and expressed as the negative logarithm.

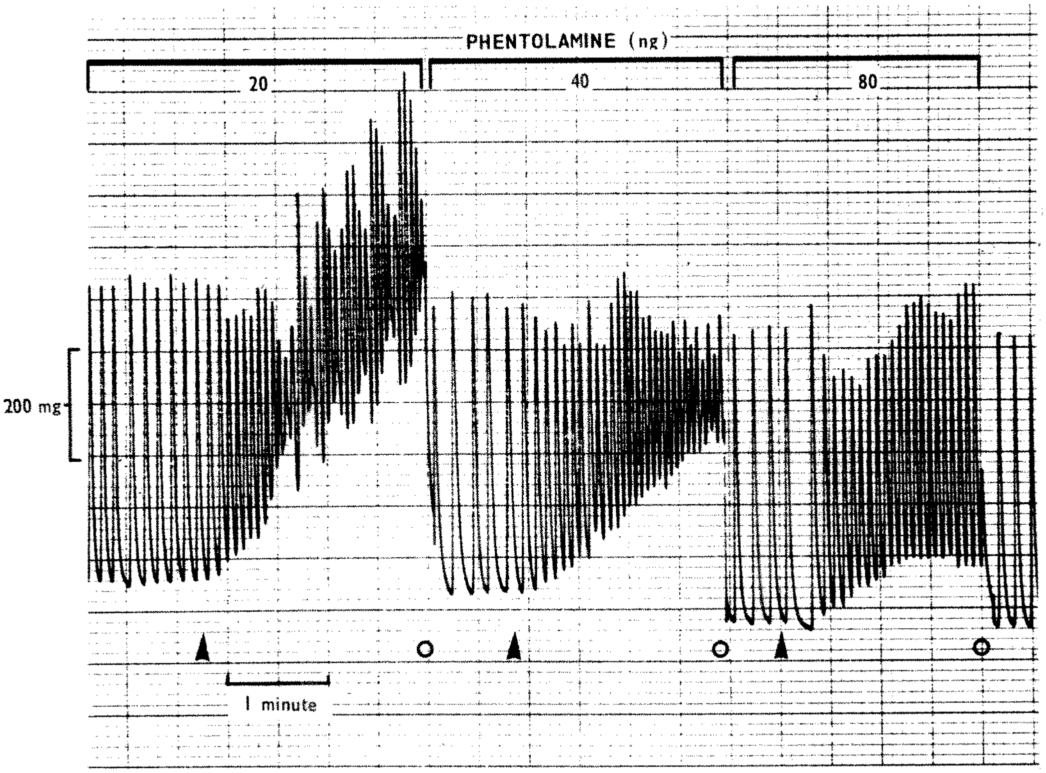

Fig. 7. Effect of equal concentrations (2 μg) of adrenaline, added at ▲, on isolated calyx in the presence of 20, 40, and 80 ng phentolamine. ○ indicates washing of the tissue with Krebs solution.

pA values obtained for phentolamine against noradrenaline and adrenaline after 10 minutes contact are presented in Table 1.

Isoprenaline acts predominantly on β-receptors, and its effect on the calyx (Fig. 3) could be abolished completely by propanolol, a selective β blocking agent, in a concentration of 1 μg/ml. Also, after pretreatment of a specimen with a large dose of phentolamine (1 μg/ml), the α stimulatory effects of adrenaline at a concentration of 8 μg/ml could be completely abolished and the latent inhibitory effects demonstrated (Fig. 9).

Acetylcholine, in a concentration of from 2 to 32 μg/ml, was found to cause stimulatory effects upon the calyx similar to those observed after treatment with the catecholamines—namely an increase in both frequency of spontaneous contraction and in resting tension (Fig. 12, A). Again the effects were dose dependent, a typical log. concentration-effect 'curve' being illustrated in Figure 10, and the pooled results of 6 experiments in Figure 11. These effects of acetylcholine (at 32 μg/ml) were greatly reduced by 2 minutes pretreatment with atropine in a concentration

Table I

pA_2, pA_{10}, and pA_2-pA_{10} Values for Phentolamine (Mean ± S.E.M.)

pA_2	Adrenaline	7·06 ± 0·04 (n = 5)
	Noradrenaline	7·11 ± 0·07 (n = 5)
pA_{10}	Adrenaline	6·16 ± 0·04 (n = 5)
	Noradrenaline	6·24 ± 0·07 (n = 5)
pA_2—pA_{10}	Adrenaline	0·90 ± 0·04 (n = 5)
	Noradrenaline	0·87 ± 0·05 (n = 5)

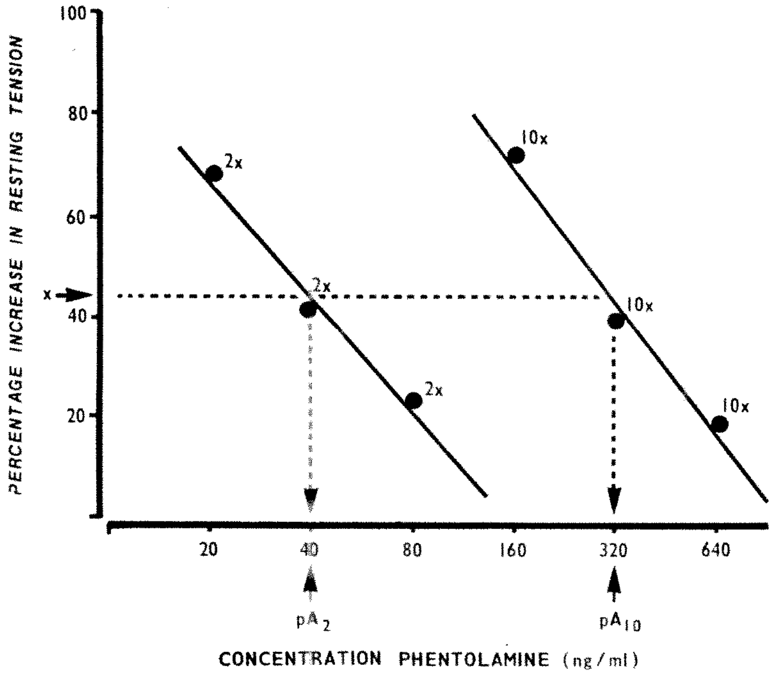

Fig. 8. Method of determining pA_2 and pA_{10} values for phentolamine. Each point represents the effect of a concentration of adrenaline ($2x$ or $10x$) on the calyx pretreated for 10 minutes with concentrations of phentolamine as shown on the abscissa. x is an approximately EC_{50} for adrenaline determined in the absence of phentolamine.

of 5 ng/ml (Fig. 12), and could be completely abolished if the concentration of antagonist was increased to 20 ng/ml.

Transmural stimulation was applied, as previously described, using a pulse width of 0·4 m seconds, supra-maximal voltage, and varying frequencies. With a frequency of 5 Hz, the tissue responded by an increase in resting tension and frequency of contraction (Fig. 13). On increasing the frequency of the stimulus, there was a corresponding increase in resting tension of the specimen, and a maximum response was obtained at 40 Hz. After having obtained such a response, tetrodotoxin[1] was added to the bath to give a concentration of 10^{-7} gm/ml. A similar electrical stimulus over the same frequency range was now found to have no effect upon the calyx. However,

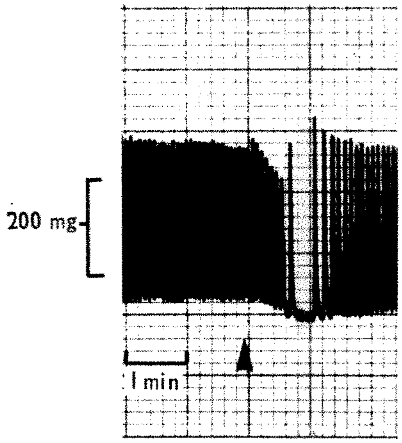

Fig. 9. Effect of 8 μg adrenaline (added at ▲) on calyx pretreated with 1 μg phentolamine.

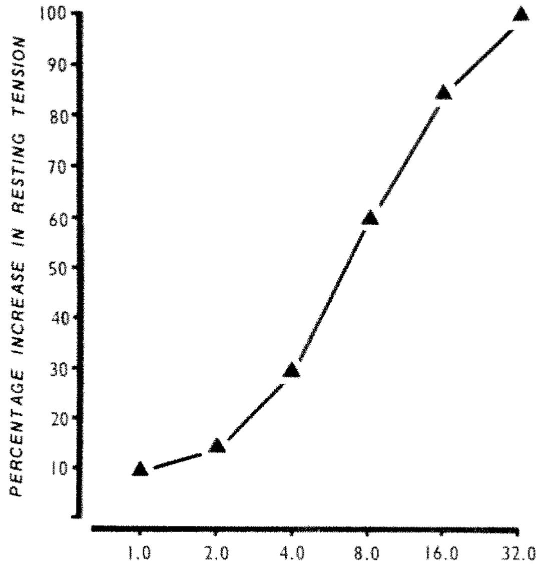

Fig. 10. Logarithmic concentration-effect curve for acetylcholine on the isolated calyx.

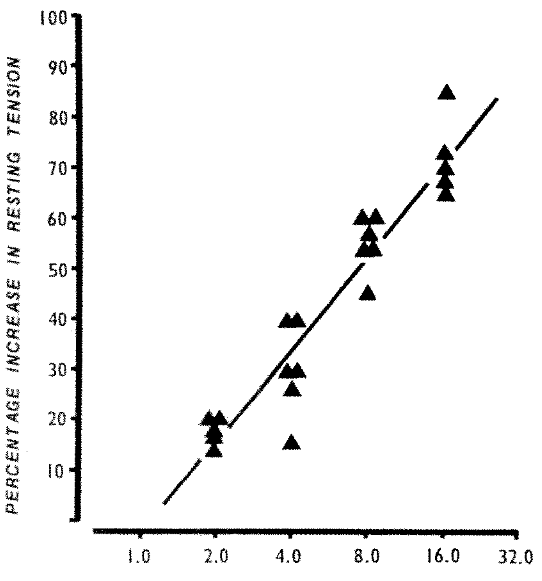

Fig. 11. Logarithmic concentration-effect line for acetylcholine. Results of 6 experiments excluding values above 90% and below 10%.

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[1] An extract of the Puffer fish capable of selectively preventing the depolarisation process in nerves.

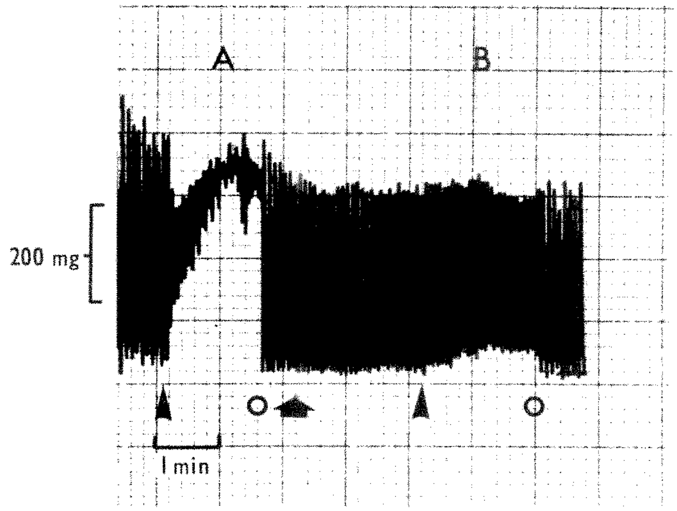

Fig. 12. Response of the calyx to 32 µg acetylcholine, added at ▲, before (A) and after (B) the addition of 5 ng atropine at 🡅.

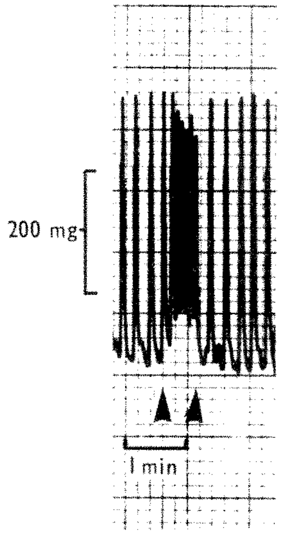

Fig. 13

Fig. 13. Response of the isolated renal calyx to transmural stimulation (5 Hz at 0·4 m seconds) applied throughout the period between the markers ▲.

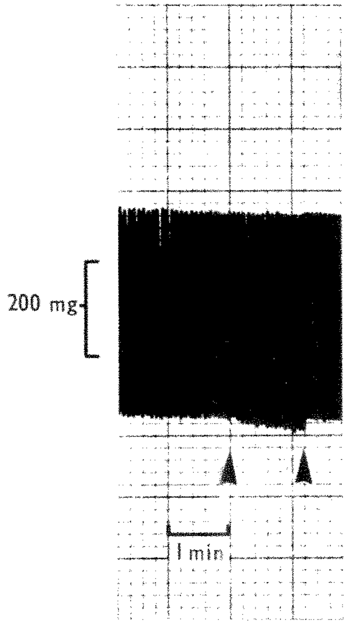

Fig. 14. Continuation of tracing from Figure 13 after treatment of calyx with 10 µg phentolamine. Electrical stimulation (40 Hz at 0·4 m seconds) was applied between the markers ▲.

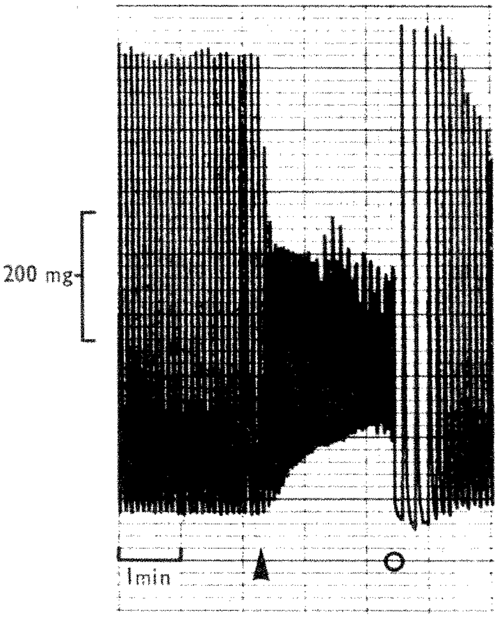

Fig. 15. Effect on the isolated calyx of 128 µg tyramine added at ▲.

the tissue remained capable of eliciting a normal response to the addition of 2 μg/ml noradrenaline. A further specimen, having first been shown to respond to electrical stimulation of 0·4 m seconds pulse width, was treated for 10 minutes with a large dose of phentolamine (10 μg/ml). Stimulation up to a frequency of 20 Hz was without effect, but as the frequency was increased up to 40 Hz, there came into effect an inhibitory action in the form of a decrease in resting tension (Fig. 14). The decrease in frequency of contraction seen with isoprenaline was not however observed under these conditions of electrical stimulation. If the pulse width was now increased to 2·0 m seconds, the tissue responded by an immediate marked rise in resting tension followed by a similar immediate return to normal on cessation of stimulation, indicating that the calyceal smooth muscle was still capable of a contractile response, most probably due to direct muscle depolarisation.

Similar experiments were carried out using high concentrations of atropine (4·0 μg/ml) to block the muscarinic receptors, but no decrease in response to electrical nerve stimulation could be demonstrated after pretreatment with this latter drug.

Tyramine has the ability to liberate noradrenaline from adrenergic nerve terminals. In doses of 16 to 128 μg/ml it caused an increase in frequency of contraction, an increase in resting tension, and a marked decrease in the amplitude of contraction (Fig. 15). Experiments were repeated after pretreating the tissue for 5 minutes with cocaine, (0·03 to 2·0 μg/ml), a substance capable of preventing tyramine uptake by the nerves. The response to further additions of tyramine was unchanged.

Finally, responses of calyx to noradrenaline were determined before and after treatment with cocaine in a concentration of 0·03 to 2·0 μg/ml. In these experiments, cocaine was used to abolish the normally occurring neuronal uptake of noradrenaline. The results showed no quantitative difference in effect, as measured by increase in resting tension, before and after treatment with this drug.

Discussion

Although the ureter has previously been subject to considerable *in vitro* study, only 3 such investigations of calyceal activity have been traced in the literature (Muschat, 1929; Finberg and Peart, 1970; Gosling and Waas, 1971). Muschat (1929) found the pig calyx to react with increased activity to addition of adrenaline. Finberg and Peart (1970) found the increased activity of the rat calyx in response to adrenaline and noradrenaline to be abolished by phentolamine. They found an inconsistent response to isoprenaline, and concluded that the actions of the catecholines were mediated solely by α-adrenoceptors. Acetylocholine was found by them to be without effect. Gosling and Waas (1971), studying rabbit calyx, obtained similar results to the above, demonstrating the presence of α-adrenoceptors but being unable to present any evidence of either β-adrenergic or muscarinic receptors.

In this present study the pig was chosen on account of the close morphological and functional similarity of its ureter and collecting system to that of man. In agreement with findings in the previously quoted studies for other species, adrenaline and noradrenaline were effective in increasing resting tension and frequency of spontaneous contractions. In addition, phenylephrine (a predominantly α-stimulating agent) caused similar effects, but as can be seen from Figure 4, failed to give the maximum response obtained with either noradrenaline or adrenaline, even at high concentrations. This may have been caused by phenylephrine acting as a partial agonist or perhaps by non-specific effects on the muscle at these high dosage levels. Evidence for the existence of partial agonists in the sympathomimetic amine group of drugs has been presented by Van Rossum (1965). Studying the α-receptors in isolated rabbit intestine he showed the (+) isomer of oxedrine to have an intrinsic activity constant of 0·8 when compared with (−) noradrenaline (intrinsic activity constant noradrenaline = 1).

The concentration-effect curves can be seen from Figure 4 and Figure 6 to be parallel and to show a potency order of adrenaline > noradrenaline > phenylephrine. This order of potency for the sympathomimetics on the calyx would suggest that the observed effects are mediated by interaction with α-adrenoceptors (Ahlquist, 1948).

The actions of all 3 drugs were antagonised by phentolamine, and the reproducible behaviour of the tissue provided by these experimental conditions allowed the antagonism to be quantified by the pA_x method. Phentolamine is a competitive antagonist at α-adrenoceptor sites, and with such antagonists, agonists acting on the same receptors should produce the same pA_x value (Schild, 1947). Receptors can hence be identified using this procedure, since tissues with similar receptors could be expected to give the same pA_x value for a given antagonist. pA_2 and pA_{10} values for phentolamine after 10 minutes contact are shown in Table 1. The mean pA_2 values did not differ greatly from previously reported values for phentolamine [7·15 rabbit thoracic aorta (Kohli, 1968); 7·18 guinea-pig seminal vesicles (Guimaraes, 1969); 6·93 cat nictitating membrane (Green and Fleming, 1967)], and it is concluded that the observed responses to adrenaline and noradrenaline were mediated by α-adrenoceptors, confirming the findings from the study of potency order of these drugs. Further confirmation can be derived from an examination of the nature of the antagonism. Arunlakshana and Schild (1959) have shown that for a competitive antagonist, the pA_2–pA_{10} difference is numerically equal to 0·95. These values (pA_2–pA_{10}) calculated from the present study are shown in Table I, and do not differ significantly from this theoretical figure (*t*-test, $P > 0·05$).

In contrast to previous workers (Finberg and Peart, 1970; Gosling and Waas, 1971), isoprenaline, a synthetic catecholamine with predominantly β stimulatory actions, was consistent in its inhibitory effect upon the spontaneously contracting calyx. This response was shown to be abolished by the selective β blocking agent propanolol, and is held as evidence for the presence of β-adrenoceptors in this tissue.

Again, in contrast to studies on the rabbit and rat, acetylcholine was found to be consistent in producing excitatory effects upon the pig calyx. The antagonism of this action by atropine suggests the effects to be mediated via muscarinic receptors present in the smooth muscle fibres.

Having shown the presence of receptor sites for both adrenergic and cholinergic neurotransmitter substances, it was next attempted to define whether or not these receptors are innervated. Three sets of experiments were performed. Electrical stimulation of the tissue was carried out using a current of pulse width such as to cause depolarisation of nerve fibres but not smooth muscle cells. The effects produced by this stimulus were an increase in resting tension and an increase in frequency of contraction (Fig. 13). They could be abolished by pretreatment of the tissue with tetrodotoxin, this finding being suggestive of a neuronally induced response. Further proof of this was offered by the observation that tissues so treated with tetrodotoxin still remained capable of responding in their usual manner to exogenous noradrenaline. There was a qualitative similarity in the tissue's response to electrical stimulation and to exogenous noradrenaline. Furthermore, stimulation of a preparation after α-adrenoceptor blockade with phentolamine resulted in replacement of the excitatory response by a slight inhibitory effect. If, however, the pulse width of the current was then increased, a direct muscle stimulatory response could still be obtained. Muscarinic receptor blockade with atropine did not affect the response of the calyx to electrical stimulation, and the conclusions from the above are that nerve stimulation was effective by liberation, from adrenergic nerves, of noradrenaline which then acted upon α-adrenoceptors on the smooth muscle of the calyx. The relaxant response to electrical stimulation, demonstrated after pretreatment with phentolamine, may have been caused by activation of β-adrenoceptors in the vicinity of the released noradrenaline, or may possibly represent a direct β receptor innervation.

Experiments were next conducted to ascertain the effect of tyramine on the calyx. The latter is a sympathomimetic amine and acts predominantly by the release of noradrenaline from sympathetic post-ganglionic nerve endings. In this study, its addition to the organ bath fluid in high concentrations caused a response similar to α-adrenoceptor stimulation. However, pretreatment of the tissue with cocaine (thus preventing the neuronal uptake of tyramine) did not alter this response, and it was concluded that the effect upon the calyx was direct upon smooth muscle cells and unrelated to noradrenaline release.

After liberation of noradrenaline from adrenergic nerves, the major route of inactivation is an active re-uptake process by the nerve terminals. Not only does this uptake process apply to the intact animal, but also to exogenously administered noradrenaline on an isolated tissue preparation. Abolition of neuronal uptake can be obtained by treating the tissue with cocaine, which prevents active transport of noradrenaline from the extra-cellular fluid to the intra-axonal storage areas, and which thereby potentiates the effect of this drug. However, in the present study, no quantitative difference in response of the calyx to noradrenaline could be determined before and after treatment with cocaine. Having already given, by electrical stimulation studies, positive evidence of innervation of the α-adrenoceptors, then the results from experiments with cocaine and tyramine suggest that the innervation is relatively sparse. This finding would be in keeping with anatomical studies of the region (Dixon and Gosling, 1973).

Summary

Isolated strips of pig renal calyx undergo spontaneous rhythmical changes in tension.

Noradrenaline, adrenaline and phenylephrine mediate their stimulatory effects by interaction with α-adrenoceptors, and isoprenaline its inhibitory effect via β-adrenoceptors.

Acetylcholine exerts a similar excitatory action via muscarinic receptors.

Evidence is presented for innervation of the α-adrenoceptors, although this innervation appears to be relatively sparse.

I am indebted to Mr Thomas Moore for his continued interest and encouragement in this project. I would also like to express my sincere thanks to Dr B. Cox, Department of Pharmacology, University of Manchester, for his invaluable assistance and enthusiasm throughout the preparation of this paper.

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Hydatid Cysts of the Kidney

Simulating Similar Kidney Lesions

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Hydatid disease is a tapeworm infection that occurs in its adult stage in the intestines of dogs, wolves and foxes and in its larval stage in sheep, hogs, cattle and occasionally in man. Thus the disease is common in sheep raising areas, as in South America, Australia, New Zealand, South Africa, Asia, Africa, countries along the Mediterranean and in the Middle East countries of which Iraq is one, but with the ease of travelling and immigration at present, it could be seen in patients all over the world (Henry *et al.*, 1966).

Table I (From the *Journal of the Indian Medical Association*, 1970) shows the world incidence of hydatid disease.

The number of hydatid disease cases seen in the last decade at the Republic Hospital and the Medical City of Baghdad was 1,346; 57 of these had involvement of the kidney. Table II shows the organ distribution of these cases.

The sex distribution is shown in Table III.

Table I

Country	Average No. of Cases Detected Early
Greece	590
Italy	459
Argentina	405
Uruguay	400
UK	90
New Zealand	87
Australia	50
Lebanon	63
India	27
USA	5
Iceland	1
Republic Hospital and Medical City, Baghdad	135

Table II

Site of Cyst	Percentage
Liver	52
Lungs	20
Kidneys	5
Brain	4
Spleen	4
Bones	11
Other parts of the body	4
	100

Table III

Sex	Number of Patients	Percentage
Male	511	30
Female	835	70
Total	1,346	100

Clinical Manifestations

Hydatid disease in the kidney as elsewhere is slowly progressive and insidious in its development; generally there are no symptoms for many years and frequently the disorder becomes apparent only as an incidental finding on routine clinical examination.

The symptoms and signs may be divided into general and local. General manifestations are rare, consisting of gradual loss of strength, loss of weight and occasionally urticaria from anaphylaxis (Deliveliotis, Kahayas, and Varkarakis, 1968).

The blood picture may show a slight elevation of the eosinophil count; this is usually slight, but occasionally may rise to 20%.

Locally a tumour mass in the kidney may be present.

The typical definite diagnostic symptoms and investigations which lead to the diagnosis are: hydatiduria (passing of daughter cyst in the urine), calcification of the outline of the cyst on X-ray; a renal mass of cystic type on I.V.P.; and positive Weinberg and Casoni tests.

The following cases were sufficiently atypical for hydatid disease of the kidney not to be considered in the differential diagnosis.

Case 1. N. K., 7-year-old girl. Her mother noticed a swelling of the left loin while bathing her. She was seen by a general surgeon. After intravenous pyelography a tentative diagnosis of Wilms' tumour was made and the patient was referred to this department. A left ascending pyelogram gave a similar picture to that of the I.V.P. (Fig. 1): a large mass replacing the upper and middle calyceal system, compressing the lower calyces and displacing the ureter medially. We agreed with the original diagnosis.

The peritoneal cavity was explored through a left paramedian incision. A large very hard and vascular tumour mass involving most of the kidney with adhesions to the peritoneum and descending colon was found. After clearing the tumour mass the kidney pedicle, which was surprisingly free from adhesions, was easily clamped and ligated. On section of the kidney a large hydatid cyst was revealed (Fig. 2).

Case 2. Y. M., a 17-year-old male. Complained of recurrent right renal colic accompanied by dysuria and interruption of the urinary stream for the past 5 months.

Clinical examination revealed only slight tenderness in the right renal angle. Other physical clinical and laboratory findings were within normal limits. Urine: 10-15 wbc, and few rbc/hpf. Culture: negative. X-ray findings: K.U.B.

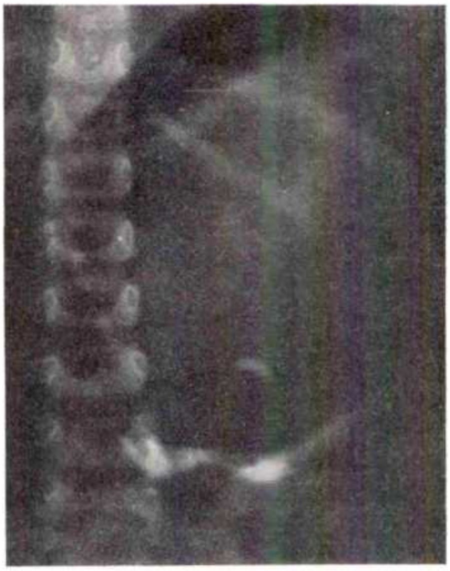


Fig. 1. Case 1. Left ascending pyelogram showing large left renal mass.

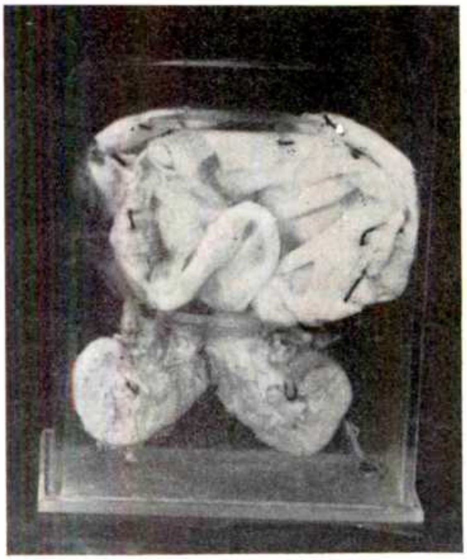


Fig. 2. Case 1. Kidney showing large hydatid cyst.

negative, I.V.P. both kidneys functioned normally, the only abnormality being some blunting and erosion of the upper minor calyces on the right side (Fig. 3). No typical cystic changes were seen. The lesion suggested tuberculosis as a possible cause. Urine culture for tubercle bacilli was negative. Ascending pyelography of the right kidney confirmed the same changes as the I.V.P. Conservative treatment with analgesics, antispasmodics and wide-spectrum antibiotics did not prevent the recurrence of the renal colic.

While exploration of the right kidney was being contemplated, the patient had another colic after which he noticed the passage of pale yellow marble-like structures in the urine which suggested that the structures could be daughter hydatid cysts. Casoni and Weinberg tests were performed with positive results. An eosinophil count was confirmed to be normal.

The right kidney was explored: a small hydatid cyst was seen involving the upper calyces and opening into the pelvis. A nephrectomy was performed. (Fig. 4).

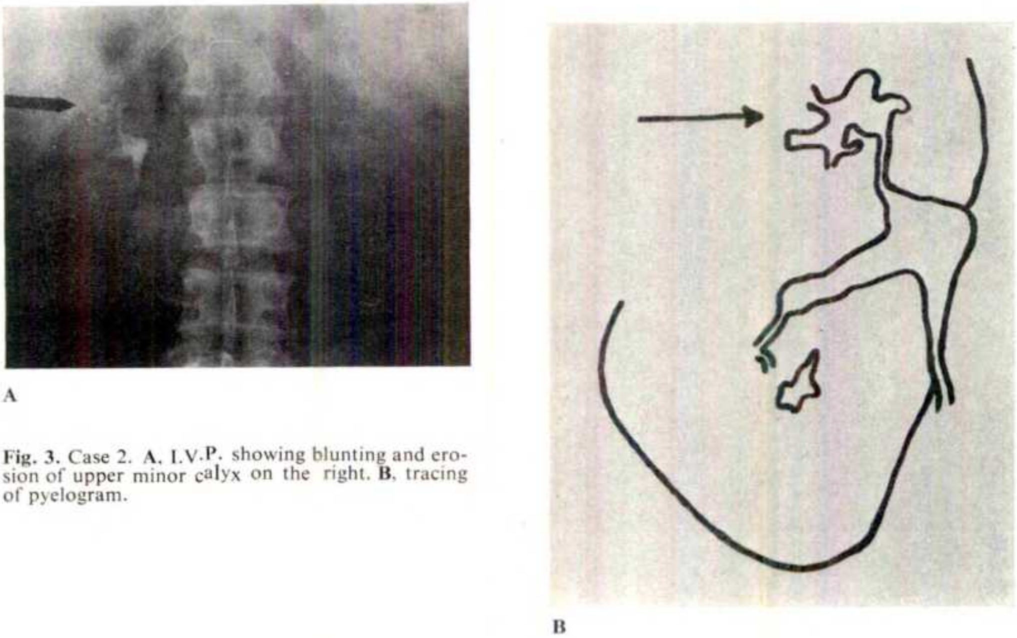


Fig. 3. Case 2. **A**, I.V.P. showing blunting and erosion of upper minor calyx on the right. **B**, tracing of pyelogram.

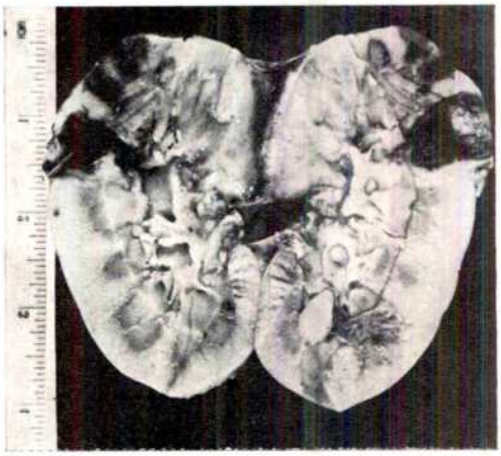


Fig. 4. Case 2. Right kidney showing hydatid cyst involving the upper calyces.

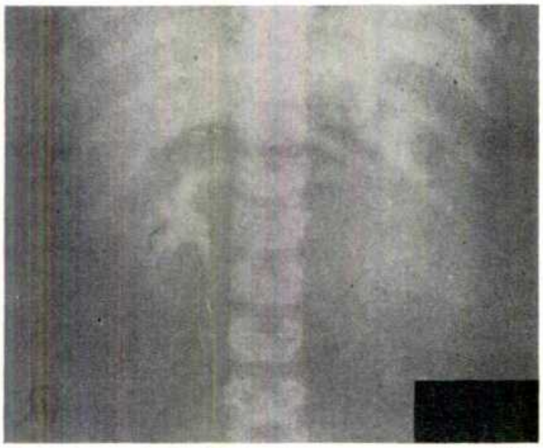


Fig. 5. Case 3. I.V.P. showing large mass occupying middle and lower parts of left kidney.

Case 3. K. G., 63-year-old male. Admitted to hospital complaining of a swelling in the left loin with dull pain at the renal angle. He had noticed the swelling for a few months; he also had occasional dysuria.

He was normotensive. The left kidney was palpable and hard. Urine: Albumin +, rbc +, wbc + +, Urine culture: growth of pyocyaneus. Blood count W.B.C. 12,600, E.S.R. 12 mm/hour. I.V.P.: Large left kidney shadow obliterating the psoas shadow. The right kidney functioned normally. The left kidney showed a dilated upper calyceal system, all the other calyces being invaded by a huge mass (Fig. 5). The patient refused aortography.

On a diagnosis of a left renal tumour the kidney was approached through the bed of the 12th rib. Following division of adhesions the pedicle was clamped and the kidney removed.

Normal kidney tissue was apparent only at the upper pole; the rest of the kidney was hard and pale grey in colour simulating a renal carcinoma. On section a large hydatid cyst was found.

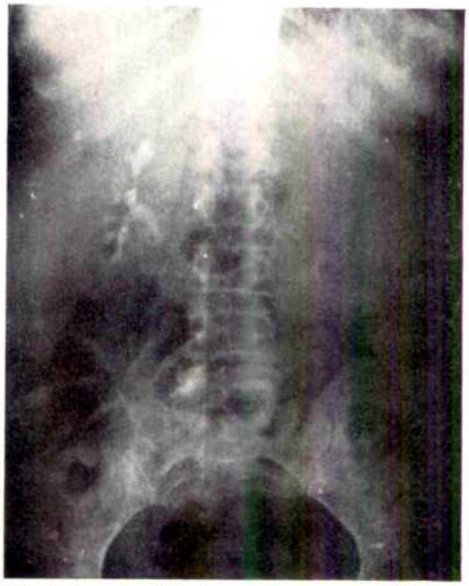


Fig. 6. Case 4. I.V.P. showing large mass left kidney —only small amount of contrast seen in lower part of left renal outline.

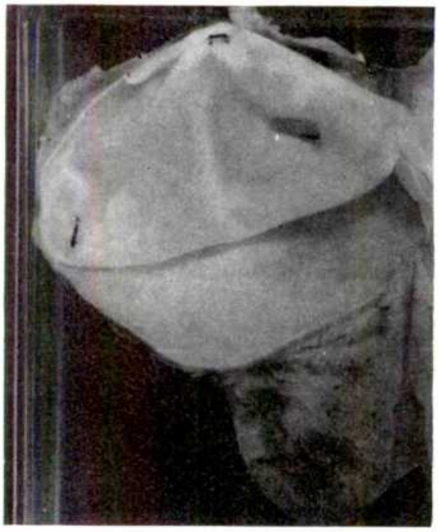


Fig. 7. Case 4. Hydatid cyst upper part left kidney.

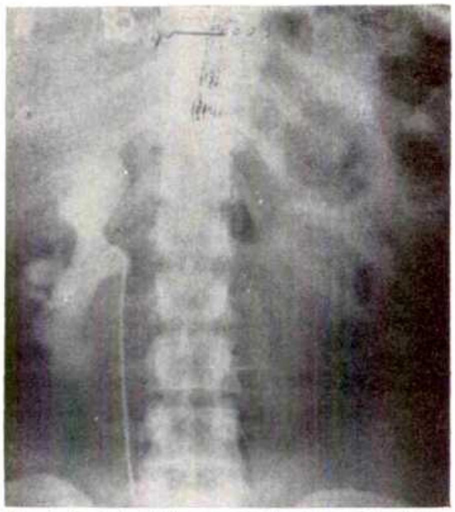


Fig. 8. Case 5. Right retrograde pyelogram showing compression of calyceal system with erosion of the lower minor and middle calyces.

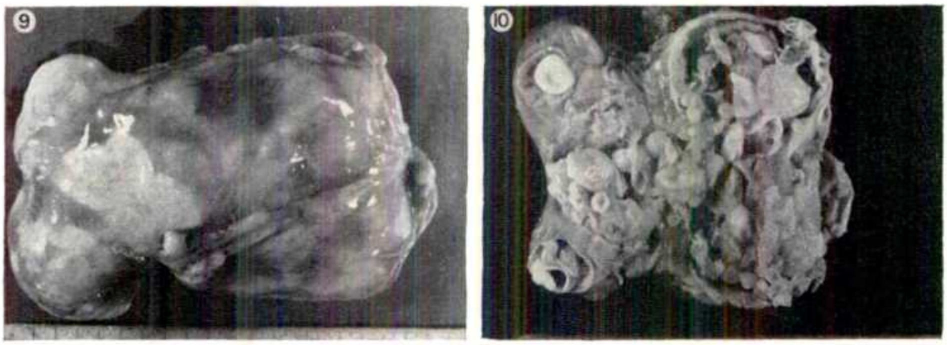
Case 4. Z. T., 40-year-old housewife. Complained of left loin pain and a mass of 3 months duration. She also had dysuria and frequency.

On examination the left kidney was palpable. Urine: wbc ++, rbc ++. Urine culture: Moderate growth of coagulase positive staphylococci. Blood picture normal. E.S.R. 12 mm in the hour. Chest X-ray: Healed tuberculous lesion of the right lung. I.V.P.: Large left kidney shadow, no calcification. No opacities. Right kidney normal. Left kidney showed contrast only in the lower calyces (Fig. 6). On retrograde pyelography the contrast did not pass beyond the uretero-pelvic junction.

With the provisional diagnosis of a tumour, the kidney was explored and a large hydatid cyst occupying the whole kidney except the lower pole was found (Fig. 7). Nephrectomy.

Case 5. N. S., a 35-year-old woman. Complained of right flank pain and swelling of 8 months duration. Apart from the hard right palpable kidney, other clinical physical and laboratory findings were within normal limits. I.V.P. showed a large right kidney outline. Left kidney normal. Right kidney showed no function. Right retrograde pyelography; compression of the calyceal system with erosion of the lower minor and middle calyces (Fig. 8).

On a preoperative diagnosis of a right renal tumour, right nephrectomy was performed. On section a large hydatid cyst was found (Figs 9 and 10).



Figs 9 and 10. Case 5. Right kidney showing (9) a large cyst on surface, (10) numerous sort of cysts on section.

Comment

The triad, pain, haematuria and tumour mass representing the common symptoms of carcinoma of the kidney are not always present; only 55% of these tumours give symptoms; in 45% the discovery is accidental. 55% present one of the triad of symptoms, 60% produce haematuria, 70% a palpable mass and 80% pain (Deming and Harvard, 1970).

In cases 1, 2, 4 and 5, the 2 common symptoms of mass and pain were present. Clinically the masses were hard and fixed, unlike other cystic conditions of the kidney; this was due to the fibrotic and sometimes calcified wall of the hydatid cyst.

Angiography was omitted from the preoperative diagnostic methods, because we thought we had sufficient evidence from the clinical and other X-ray findings to make a diagnosis of tumour of the kidney.

In case 2 the preoperative diagnosis was of an infectious lesion, possibly tuberculous, which led to corresponding preoperative investigations.

Summary

Five cases of atypical hydatid cyst of the kidney are present.

Four cases simulated kidney tumours and 1 an infectious lesion, but were misdiagnosed on account of the absence of the typical signs and finding of hydatid disease.

With the increase in world travel hydatid disease should be included in the differential diagnosis of all other kidney masses, especially when they are atypical.

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Calcium-47 Absorption in Urolithiasis

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An association between high urinary calcium and calcium urolithiasis was described by Flocks in 1939 but subsequent work has fallen short of establishing the exact relationship between these 2 phenomena. In a group of patients forming calcium-containing renal stones, Melick and Henneman (1958) found that 32% had hypercalciuria. Similar findings have been made by others. Whilst an excessive urinary calcium is present in other specific diseases, hypercalciuria as a phenomenon occurring in the absence of any of these was described by Albright *et al.* (1953). This syndrome of idiopathic hypercalciuria was defined as the occurrence of a high urinary calcium in association with normal serum calcium, a tendency to hypophosphataemia and renal stone formation and it has since been recognised by others.

Caniggia, Gennari and Cesari (1965) suggested that the hypercalciuria was primarily absorptive in origin. Peacock, Hodgkinson and Nordin (1967) showed the importance of dietary calcium in demonstrating hypercalciuria, suggesting that the hypercalciuria in stone formers was probably due to excessive absorption of calcium. An implication of this was that idiopathic stone formers were largely drawn from that segment of the population in which absorption and therefore urinary excretion of calcium was above average.

This paper is concerned with the study of a group of stone formers and recurrent stone formers in the Royal Navy in whom intestinal calcium absorption has been measured by arm counting using calcium-47 (^{47}Ca).

In the past, techniques for assessing calcium absorption have required the patient to be in hospital and on a strict metabolic regime and have also required accuracy in the timing and collection of urine, faecal and blood samples. With the availability of ^{47}Ca, a gamma-emitting radio-nuclide with a half-life of 4·53 days, a relatively simple and accurate method of measuring calcium absorption has become available using external scintillation counting (Curtis, Fellows and Rich, 1967; Wills *et al.*, 1970; Macleod, 1971).

Methods

All the cases of urolithiasis studied were registered in the Royal Naval Renal Stone Survey, which is supported by grant from the Medical Research Council, and all had a full general and metabolic investigation and excretion urography performed.

The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least 4 separate occasions with the patient in the fasting state. Serum calcium was measured by auto-analyser using Technicon Method N3b and the upper limit of normal for this laboratory was taken as 10·5 mg/100 ml.

Urinary calcium excretion was measured first of all with the patient on a diet containing calcium supplements since it has been established that hypercalciuria is only detectable at moderately high calcium intakes (Knapp, 1947; Peacock, Hodgkinson and Nordin, 1967). Thereafter a low calcium diet (150 mg calcium per day) was given and, after a period of 3 days, further measurements of calcium excretion were made to establish the response to this. Urinary calcium was estimated by atomic absorption spectroscopy using the Unicam SP 90.

Gastro-intestinal absorption of radioactive calcium was measured by an arm-counting technique following separate intravenous and oral doses of ^{47}Ca chloride (Macleod, 1971). This method is based on the assumption that the distribution in the body of the absorbed part of an oral dose of calcium is identical to that of an entire intravenous dose; thus the fraction of a known intravenous dose, measured in the forearm in this case, will be the same as that of the absorbed dose. Since it has been reported that restriction of calcium intake, as in a low calcium diet, will increase the avidity of the absorptive processes for calcium (Malm, 1958; Heaney and Skillman, 1964; Lloyd, 1967) both a control group and the patients prior to January 1972 were on a normal diet except for a fast of 12 hours before receiving the oral dose of ^{47}Ca on the 2nd day of the test. For various reasons during 1972, 49 of 83 patients so tested had started a low calcium diet of 150 mg of calcium per day at the time of the investigation. Of these, the great majority had calcium absorption measured within a day or two of starting the low calcium diet and in no case was the measurement made with the patient more than 5 days on this diet. Comparing the 2 groups, the results showed no statistical difference; 63% of patients on the low calcium diet and 60% of the patients on a normal diet were absorbing calcium excessively. This suggests that a low calcium diet for a short period of time does not influence the process of absorption from the gut. This finding agrees with the observation of Wills *et al.* (1970).

Table I

^{47}Ca Absorption in Controls

	Percentage Calcium Absorption		
Subject	March 1970	January 1971	July 1972
R. M.	32	...	...
I. L.	30	29	36
H. G.	28	...	...
D. M.	30	...	...
R. L.	26	30	...
P. C.	28	...	...
R. C.	...	26	...
D. S.	29	...	36
P. B.	25	27	26
P. G.	31	...	29
B. G.	...	35	...
D. J.	...	...	36
S. D.	...	...	36
H. P.	...	...	36
N. S.	...	...	35
P. L.	...	...	35
J. S.	...	...	26
A. K.	...	...	25
G. T.	...	...	27
P. C.	...	...	33

Since the publication of the paper describing this technique (Macleod, 1971) the original 10 control subjects have been augmented by an additional 10 and measurements have been repeated on the previous controls over a period of 3 years. Results in these showed that the amount of the oral calcium dose absorbed from the intestine was between 25% and 36% with a mean of 30% (see Table I).

Results

125 cases of urolithiasis were studied. Only 2 of this number were female.

Of the 125 patients, 23 (18%) absorbed calcium within the normal range; 102 (82%) absorbed it excessively. The extent of this hyperabsorption of calcium was variable and is shown graphically in Figure 1. Estimations were repeated in a number of these patients over an 18-month period and these showed that the tendency to absorb calcium excessively remained although there was some variation of the extent of this (Table II).

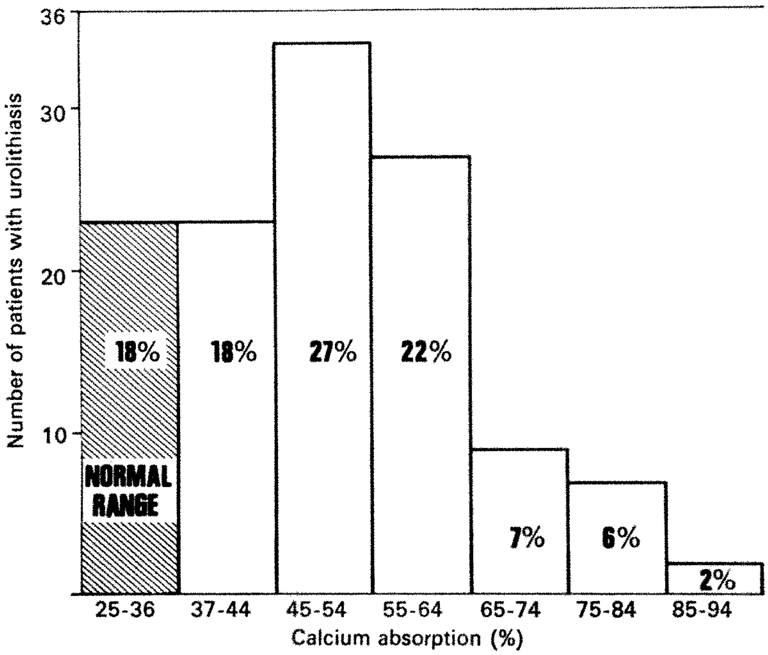

Fig. 1. Variable intestinal hyperabsorption of ^{47}Ca in 125 cases of urolithiasis.

Table II

Interval Estimations of ^{47}Ca Absorption in Known Hyperabsorbers

Subject	^{47}Ca Absorption 1		^{47}Ca Absorption 2	
		%		%
T. G. H.	16.11.70	74	13.9.71	60
E. J. H.	16.11.70	64	13.9.71	51
P. J. D.	14.12.70	76	19.6.72	52
B. L. P.	10. 5.71	77	19.7.71	71
H. J. T.	7. 9.70	44	19.7.71	41
J. F.	20. 9.71	76	10.7.72	55

A comparison of calcium absorption with 24-hour urinary calcium excretion in the 125 patients showed that all but 3 who were hypercalciuric were also absorbing calcium excessively from the intestine (Fig. 2). This confirms observations by others (Flocks, 1939; Zisman, Pak and Bartter, 1967; Wills *et al.* 1970).

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Two subgroups were formed from the series for comparison. The first was of patients who had formed only a single stone at the time of investigation. The second group comprised those who had formed 2 or more stones in clearly separated instances and were therefore recurrent stone formers. The first group may represent the type of patient in whom stone formation is an isolated incident but it is recognised that with a sufficiently long follow-up period some of these could have recurrences at a later date. In other respects both groups appeared to be well matched; the mean age of the single stone formers was 31 years and that of the recurrent stone formers 34. The difference in mean age was not significant.

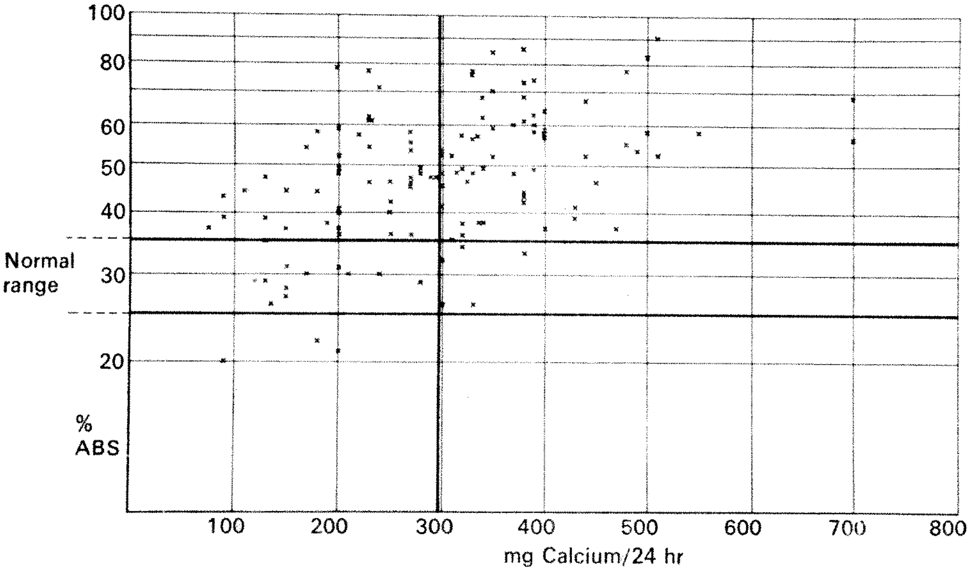

Fig. 2. Comparison of ^{47}Ca absorption with 24-hour urinary calcium excretion in 125 cases of urolithiasis.

		47 Ca Absorption >36%	Urinary Ca^{++} Excretion >300 mg/day
Solitary stone	78	59 (76%)	31 (40%)
Recurrent stone	47	42 (89%)	36 (77%)

Fig. 3. Comparative incidence of increased ^{47}Ca absorption and hypercalciuria in solitary and recurrent stone cases.

Of 78 cases of apparently solitary stone, 59 (76%) showed excessive intestinal calcium absorption and 31 (40% of the total) were hypercalciuric. Of 47 cases of recurrent urolithiasis, 42 (89%) absorbed calcium excessively from the intestine and 36 (77% of the total) excreted calcium excessively in the urine at the time of investigation (Fig. 3).

In the single stone formers the mean calcium absorption was 46% (S.D. 13) and the mean 24-hour urinary calcium excretion was 276 mg (S.D. 116). In the recurrent group, mean absorption was 56 (S.D. 16) and mean excretion 346 mg (S.D. 104). The comparison between the 2 groups shows a significant difference (x^2 test to one degree of freedom, $P < 0{\cdot}025$) even with the probability of "contamination" of the first group with a number of potential recurrent stone formers (Fig. 4).

	Mean 47 Ca absorption	Mean urinary Ca^{++} excretion
Solitary stone	46% (S.D. 13)	276 mg/day (S.D. 116)
Recurrent stone	56% (S.D. 16)	346 mg/day (S.D. 104)

$P < 0{\cdot}025$

Fig. 4. Comparison of mean ^{47}Ca absorption and urinary calcium excretion in solitary and recurrent stone cases.

Discussion

Hypercalciuria has been found to occur in approximately one-third of cases of calcium-containing renal stone in a previous review of cases of urolithiasis in the Navy. The incidence in the present series is 54% but this is a spuriously high figure since the recurrent stone former will tend to be referred to this hospital for full investigation more often than the patient with a single, short-lived incident. Excessive urinary calcium excretion has been ascribed to excessive intestinal calcium absorption (Pyrah, 1958; Harrison, 1959; Parfitt *et al.*, 1964; Peacock *et al.*, 1967). The results from the ^{47}Ca absorption studies support this concept. They show that a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis.

There is only partial correlation between excessive intestinal absorption of calcium and the occurrence of hypercalciuria. All but 3 of the hypercalciurics were found to absorb calcium excessively but 49 patients who were absorbing calcium in excess from the intestine were excreting calcium in normal amounts in the urine at the time of test. Since the ^{47}Ca absorption test deals only with the percentage absorption of a calcium load it is possible that the normal excretion resulted from a low calcium intake. All patients, however, were on a standard ward diet with calcium supplement in the form of a pint of milk per day besides that taken with cereal, tea and coffee. In the circumstances, if there was a simple linear relationship between calcium uptake and excretion, greater correlation might have been anticipated. However, since hypercalciuria is assessed on the amount of calcium in a 24-hour collection of urine, diurnal variations of calcium concentration will not be apparent; thus, hypercalciuria of varying degree may occur on a number of occasions within a 24-hour period without there being necessarily overall hypercalciuria (Marshall, 1972). It may therefore be inadequate to define hypercalciuria as the excretion of more than 300 mg of calcium in 24 hours in the male and 250 mg in the female (Hodgkinson and Pyrah, 1958). Rose (1967) has pointed out that the normal range of urinary calcium varies from one country to another and may also vary within a country since Watson and Dale (1966) consider that in London the excretion of up to 400 mg of calcium per day is normal for a man and 300 mg per day for a woman.

In this series, however, there appears to be closer correlation between the intestinal calcium uptake and urinary calcium excretion in the recurrent than in the apparently solitary stone formers.

An implication of the finding of an increased absorption of calcium in a high proportion of cases of urolithiasis is that greater quantities of calcium are being presented to the excretory system and the nephron in particular for excretion. With its known toxicity when present in excess, cellular damage due to high local concentrations of calcium might occur in the cells of the nephron or its interstitial tissues. This may be an interpretation of the finding by Anderson (1968) of foci of calcium phosphate precipitation in the kidneys of patients with a history of renal stone. Similar foci were present in patients who had no history of stone formation but were significantly more prevalent in the stone-forming group in which they occurred in 64%. Malek and Boyce (1973) describe calcium deposits in the kidneys of all of 52 cases of idiopathic calcium oxalate stone. These observations bear comparison with the present finding of excessive intestinal absorption of calcium in 82% of this group of stone formers.

In Anderson's series the calcium phosphate was present within the interstitial tissues and the epithelial cells of the renal tubules, sometimes extending into the lumen; the loop of Henle and the collecting tubules were most frequently involved. Boyce (1972) in a study of biopsies of human kidney found Periodic Acid Schiff (PAS) positive material, usually with concentric laminar structure and containing calcium in significant quantities, within the lumen of the nephron. He considered that the origin of this material was in the proximal renal tubule and that there was subsequent migration to the collecting ducts. He attributed the high incidence of medullary concretions to the coalescing ductal anatomy. Cooke (1972) in a radio-isotope study demonstrated a marked calcium concentration gradient ranging from maximal in the papilla tip to minimal in the cortex of the kidney; he also found differences in the calcium content of anatomically comparable regions of the kidney when he compared specimens from a population group with and another without a tendency to form renal stones.

It is well known that calcium salts tend to be deposited in tissues which are already damaged or undergoing degeneration. Scarparelli, Tremblay and Pearse (1960), in drawing attention to this, pointed out that the damaging agent in some cases could be an excess of calcium itself. Cells which are involved in the metabolism or transport of calcium—as are the cells of the nephron—are probably protected against its toxic effects within certain limits. An excess of calcium, however, may overwhelm a protective mechanism and result in tissue damage and subsequent calcium deposition.

The lesions described by Anderson (1968) and others may therefore be primary and stone formation in the tubules and calyces a secondary phenomenon due to crystallisation on a calcified nidus extruded from the epithelium of the tubules. They may be a direct consequence of a metabolic abnormality resulting in the increased intestinal absorption of calcium as found in such a high proportion of this series of stone formers.

Summary

The intestinal calcium absorption was measured in a group of stone formers using an external isotope counting technique.

Hyperabsorption was found in 82% and was even more prevalent in the recurrent cases.

Comparison of absorption with urinary calcium excretion showed greater correlation in a group of recurrent stone formers than in cases of apparently solitary stone formation.

The finding of intestinal hyperabsorption of calcium in a high proportion of stone formers may be aetiologically significant in the parenchymal calcium deposition found in these cases.

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The Effect of Cellulose Phosphate on Intestinal Absorption and Urinary Excretion of Calcium

Some Experience in its use in the Treatment of Calcium Stone Formation

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The findings in a previous paper have provided further support for regimes of treatment which reduce the intestinal uptake of calcium and therefore its urinary excretion in the management of recurrent calcium urolithiasis (Blacklock and Macleod, 1974).

Dietary measures have already been used towards this end and Nordin (1972) considers that a diet low in calcium and low in oxalates is the simplest and most effective approach in the treatment of this condition. Sodium phytate has been shown to form a relatively insoluble complex with calcium in the gut and the effect of this has been to lower urinary calcium in patients with idiopathic hypercalciuria (Henneman *et al.*, 1958); there is however an increase in urinary phosphate excretion at the same time (Parfitt *et al.*, 1964). Oral administration of sodium phosphate similarly has the effect of reducing intestinal calcium absorption and urinary calcium excretion but the urinary phosphorus excretion in the form of orthophosphate increases at the same time. Therapeutic use of both sodium phytate and sodium phosphate is therefore accompanied by a possibility of increased tendency to calcium phosphate precipitation on account of the increase in its activity product ratio. (Pak *et al.*, 1971). The thiazides as a group reduce urinary calcium excretion and increase renal excretion of phosphate as pyrophosphate with a concomitant increase in the urinary sodium and potassium. Calcium balance studies carried out at the time of thiazide treatment suggest that calcium is retained during such treatment (Lamberg and Kuhlbäck, 1959; Lichwitz *et al.*, 1961; Higgins *et al.*, 1964; Yendt, Gagne and Cohamin, 1966; Harrison and Rose, 1968).

Sodium cellulose phosphate, the sodium salt of the phosphoric ester of cellulose (Whatman Biochemicals Ltd) is an ion exchange cellulose with special affinity for divalent cations because of the steric configuration of the phosphate radicals attached to the cellulose molecule. In the stomach it exchanges sodium for calcium which is eliminated in the faeces so preventing the absorption of dietary calcium; it similarly binds with secreted calcium preventing its reabsorption. The diminution in calcium absorption is accompanied by a reduction in the renal excretion of calcium and a slight increase in urinary phosphorus but the urine saturation with brushite ($CaHPO_4 \cdot 2H_2O$), a probable nidus for calcium stones, is reduced (Pak, 1973).

This paper describes some observations on the effect of sodium cellulose phosphate on intestinal calcium uptake and urinary calcium excretion in patients with urolithiasis. Further observations are made on the results of a limited clinical application of the substance.

Materials and Methods

Clinical Data

The effect of cellulose phosphate was evaluated in a series of patients who exhibited intestinal hyperabsorption of calcium and hypercalciuria. All had full general and metabolic investigation including excretion urography. Cases of overt hyperparathyroidism were excluded.

Analytical Procedures

Intestinal calcium absorption was assessed by the technique of external radioisotope counting described in a previous paper (Macleod, 1971). The normal range of absorption established by this method was 25% to 35% of the calcium meal.

Urinary calcium excretion was measured with 24-hour specimens of urine by atomic absorption spectroscopy using the Unicam SP 90. Hypercalciuria was taken as the excretion of more than 300 mg of calcium per day in the male and more than 250 mg calcium per day in the female (Hodgkinson and Pyrah, 1958).

The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least 4 separate occasions at the outset and at each attendance for follow-up examination with the patient in the fasting state. Serum calcium was measured by auto-analyser using Technicon Method N3b and the upper limit of normal for this laboratory was taken as 10·5 mg/100 ml. Serum iron, copper and magnesium were measured at the outset in each patient and at each follow-up examination subsequently. Serum iron was measured by Richterich's method and copper and magnesium by atomic absorption spectroscopy (Unicam SP 90).

Results

Initially the effect of sodium cellulose phosphate on ^{47}Ca uptake was evaluated in various conditions of dosage and administration. In the tests described in paragraphs 1 and 2 below the sodium cellulose phosphate was taken in water within 5 minutes of an oral dose of ^{47}Ca chloride on the second day of an absorption test.

Laboratory Findings

1. In 10 patients who were given 5 g of the substance there was a marked reduction in ^{47}Ca absorption (Table I).

Table I

Effect of Cellulose Phosphate on ^{47}Ca Absorption in Cases Known to Absorb Calcium Excessively from the Intestine

	^{47}Ca Absorption	
Subject	Before CP	After CP
	%	%
K. D.	70	11
T. G. H.	60	19
R. B.	58	16
E. M. F.	76	23
B. B.	67	16
T. P.	84	26
A. M.	57	18
P. G.	77	15
C. E. B.	77	18
N. J. F.	91	32

2. The dose of the substance was varied. Two cases each received 1 and 2 g respectively and a fifth was given 3 g and then 5 g in an uptake test (Fig. 1). The effect appeared to be dose related. Five grams reduced the intestinal calcium by as much as 85% and even a 1 g dose resulted in a 50% reduction. The 5 g sachet provided as the standard dose therefore has a wide margin for effective action in this respect. Such a dose, however, is probably essential when it is considered that the substance will ordinarily be dispersed throughout a semi-solid food bolus.

Urinary calcium excretion was measured concurrently with the various dosages of sodium cellulose phosphate and appeared to be reduced commensurately with the dose (Fig. 2).

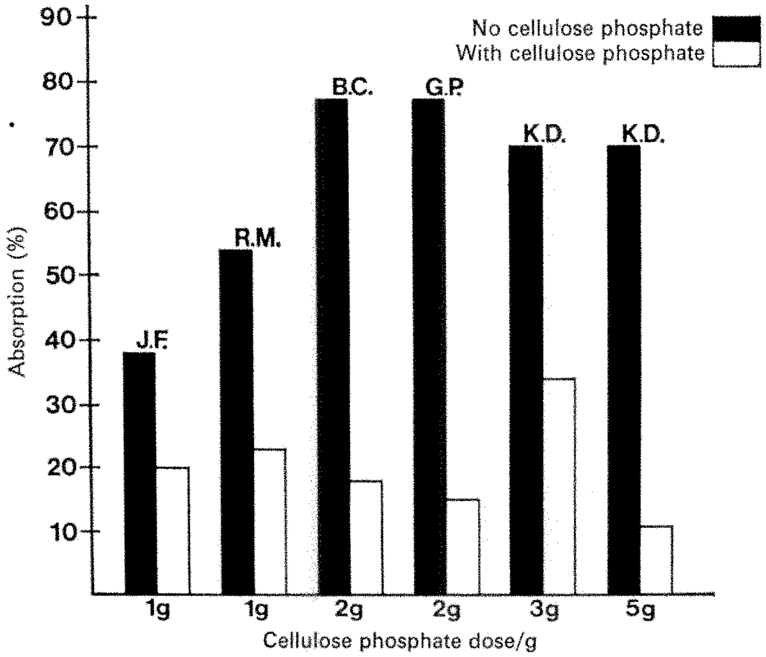

Fig. 1. Effect of variable dosage of sodium cellulose phosphate on intestinal calcium absorption.

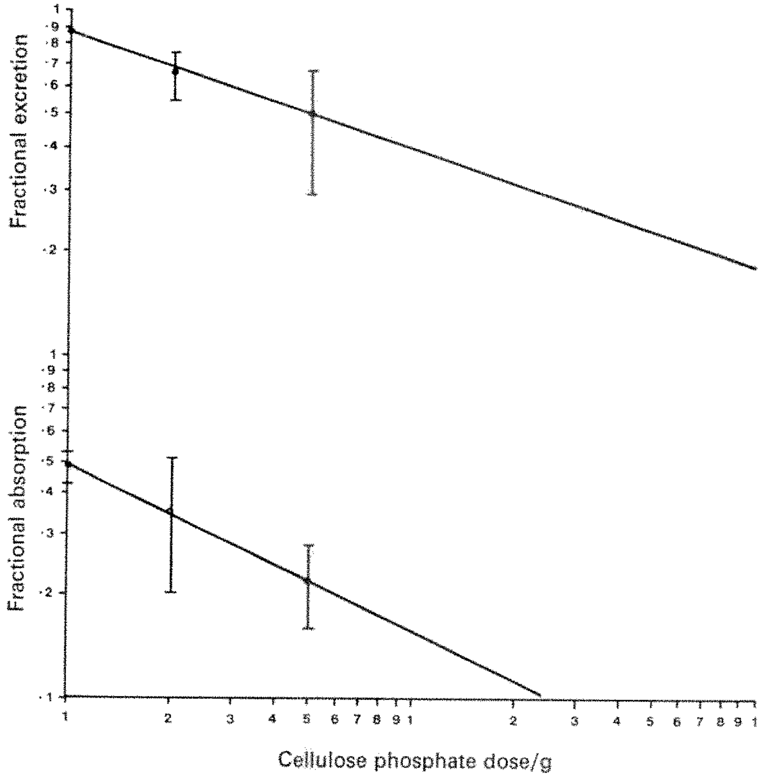

Fig. 2. Comparison of the influence of varying dosage of sodium cellulose phosphate on intestinal absorption and urinary excretion of calcium.

3. The influence on calcium absorption of taking a 5 g dose of sodium cellulose phosphate at variable intervals of time from a calcium meal was evaluated (Fig. 3).

Maximum effect was achieved if the substance was taken with a meal or within 1 hour thereafter. There was a marked reduction in effect if the substance was taken more than 1 hour afterwards. Bearing in mind that the calcium meal was in liquid form in these tests, it is likely that the dose relationship of sodium cellulose phosphate to a normal meal is even more critical.

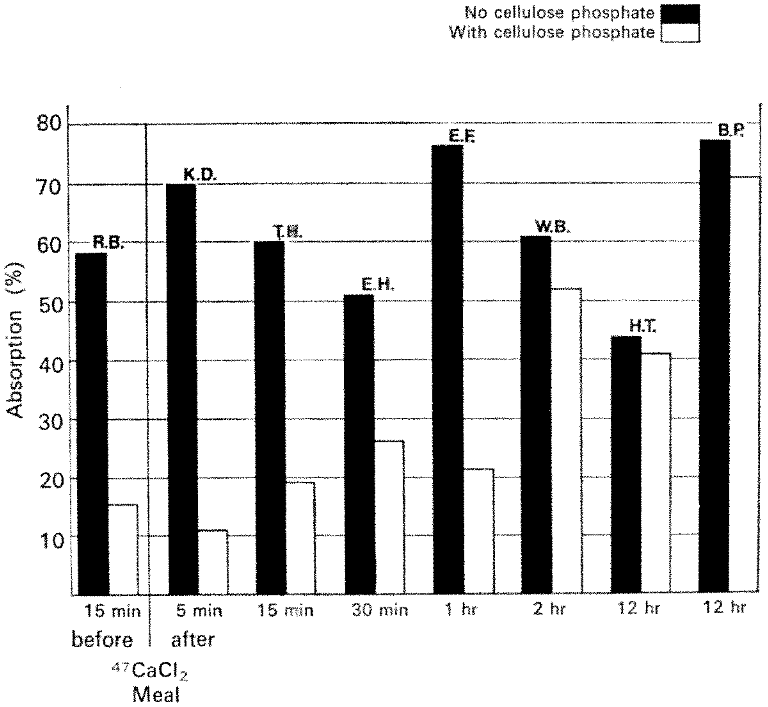

Fig. 3. The influence of time between a calcium containing meal and dose of sodium cellulose phosphate on the reduction of intestinal calcium absorption.

4. The effect of the substance on urinary calcium excretion was assessed in a number of patients with hypercalciuria of varying degree (Fig. 4). In all of these, 5 g of sodium cellulose phosphate taken 3 times daily at the time of meals, effectively reduced urinary calcium excretion to within normal levels.

5. *Other observed effects of sodium cellulose phosphate administration.* Serum levels of calcium and phosphorus were not altered in any of the patients even when the substance had been taken for a period as long as 7 years in a dose of 5 g 3 times daily.

Since the action of sodium cellulose phosphate is not selective as regards the divalent cations it can absorb, there is the theoretical possibility of trace metal deficiencies in long-term usage. Dent, Harper and Parfitt (1964) found a fall of plasma magnesium from 2·0 to 1·4 mEq/l. Pak (1973) noted a reduction in the serum concentration of magnesium and its renal excretion in a majority of cases. He found that it did not significantly affect the metabolism of copper or zinc. Pietrek and Kokot (1973) noted a trend towards reduction in the levels of serum magnesium, iron, copper and zinc concentrations although this was not statistically significant.

In the present series of cases who were treated without magnesium supplement for various periods of time there appears to have been little significant effect on plasma magnesium. One case treated for more than 4 years has a serum magnesium of 2·2 mg %; another treated for a similar period, however, has a level of 1·4 mg %.

Serum copper and iron appear to have been largely uninfluenced although no statistical evaluation of these results has been carried out. In 2 cases who have had the substance for more than 3 years the serum iron at present is 50 and 60 μg per 100 ml respectively, the lower level of normal (Fig. 5).

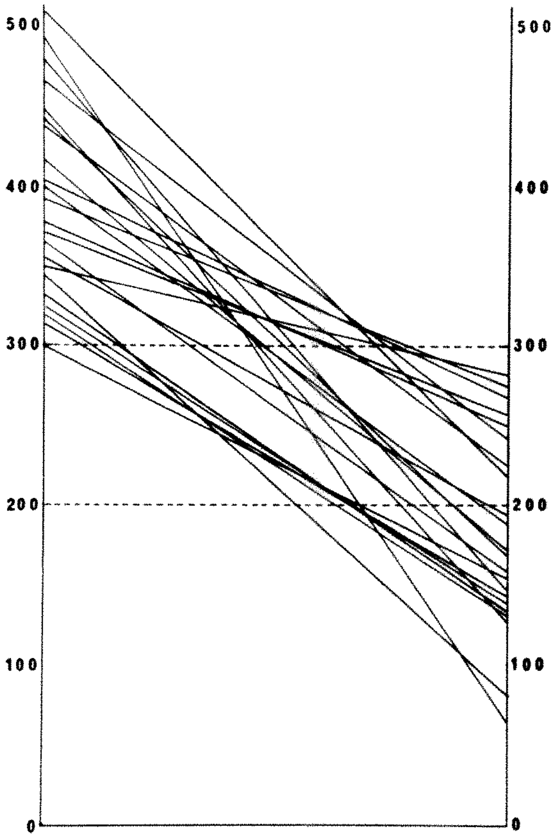

Fig. 4

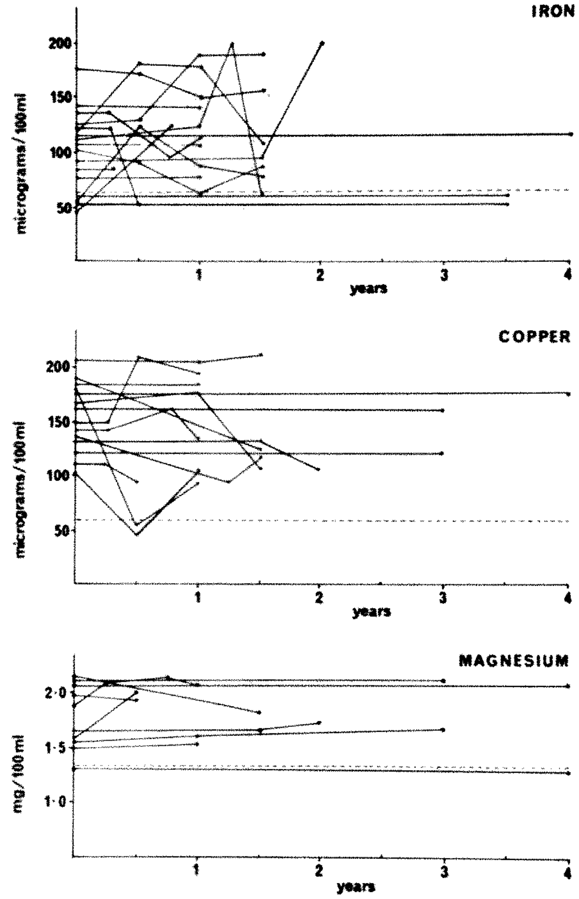

Fig. 5

Fig. 4. Effect of sodium cellulose phosphate on urinary calcium excretion in 22 cases of idiopathic hypercalciuria and stone formation.

Fig. 5. Variation in serum levels of iron, copper and magnesium with long-term sodium cellulose phosphate treatment.

Clinical Experience with Sodium Cellulose Phosphate in Recurrent Calcium Urolithiasis

All cases treated with sodium cellulose phosphate had a history of recurrent urolithiasis and were hypercalciuric. The duration of treatment up to the present time is variable, ranging from some months to several years.

Sodium cellulose phosphate is easy to take and is quite palatable. Intestinal upset and diarrhoea which had been noted by others (Harrison *et al.*, 1972) have not been encountered.

The urinary calcium excretion has been measured in a number of patients at various intervals of time from the commencement of treatment. In 2, hypercalciuria persisted but a subsequent satisfactory reduction in calcium excretion has followed supplementing the treatment with a low

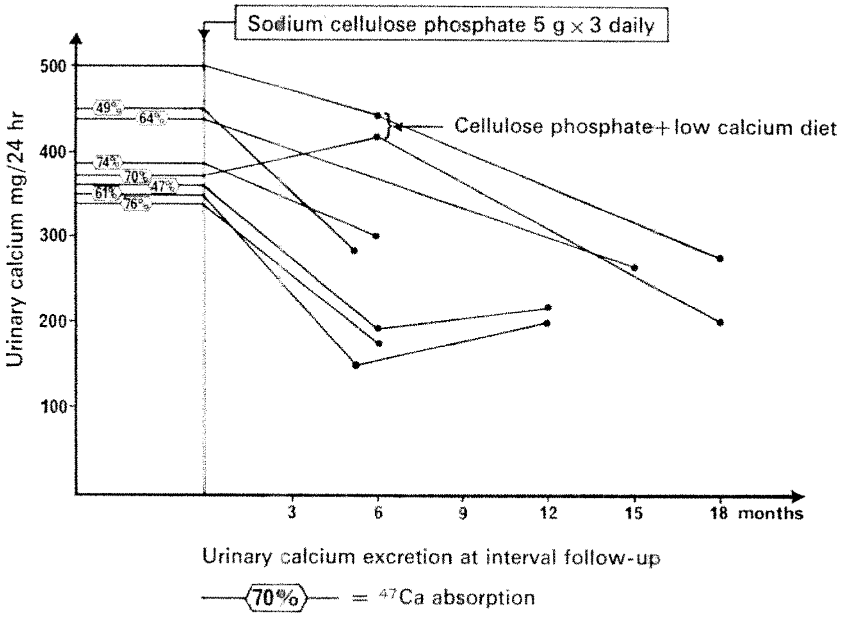

Fig. 6. Urinary calcium excretion at various intervals from commencement of treatment with sodium cellulose phosphate.

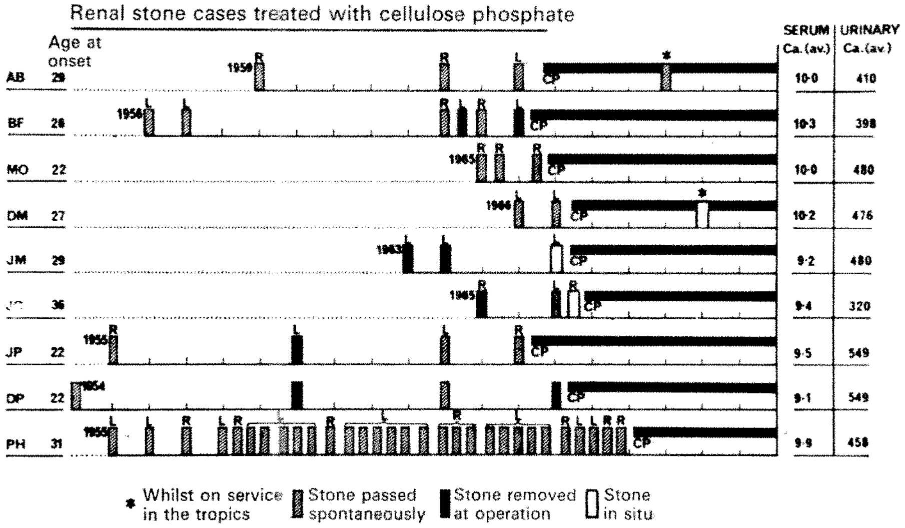

Fig. 7. Graphic representation of stone incidents in 9 cases both before and after the commencement of sodium cellulose phosphate treatment.

calcium diet. One of these cases had a ^{47}Ca uptake of 70%. The majority show a satisfactory reduction of calcium excretion to within normal rates (Fig. 6).

Pietrek and Kokot (1973) have found the urinary calcium to be maintained consistently at reduced levels but others (Rose and Harrison, 1972) have had the impression that the initial reduction is not maintained after a time. This is probably a measure of the tendency to default with treatment rather than an indication of the development of resistance in some form to its effect.

Both Pak (1973) and Pietrek and Kokot (1973) already have some evidence of a reduced frequency of stone incidence with this treatment. The effect of the preparation in a number of patients in this series who have been treated for several years is shown graphically (Fig. 7).

Only 2 new stones have been formed in the 9 cases depicted; in both of these there was an additional aggravating factor of service in a tropical climate at the time of the recurrence and both were engaged on watchkeeping duties at sea when there was difficulty in relating cellulose phosphate dosage to irregular meals. Case P. H. has shown the most significant response; this patient had consistently formed several stones annually from 1955 until the time of starting treatment with sodium cellulose phosphate in 1969; the majority of stones passed had been calcium oxalate but several were "mixed"; since the commencement of treatment there has been no further instance of urinary colic or passage of a stone and his urinary tract is demonstrably clear of opaque calculi at the present time, *i.e.* 1973. No other therapy or dietary means of control has been adopted by this patient in the meantime. No statistical evaluation of this series has been attempted at this time.

Discussion

Previous work (Blacklock and Macleod, 1974) has shown excessive intestinal absorption of calcium in a significantly high proportion of calcium stone formers. In a group of apparently solitary stone formers 76% absorbed calcium excessively. In a series of recurrent stone formers, 89% showed excessive calcium absorption. Hypercalciuria occurred in 40% of those with an apparently solitary stone and in 77% of those who had formed more than one calcium stone. These findings provide further support for a rationale of treatment directed at reducing intestinal calcium absorption and, through this, the renal filtered load of calcium and the urinary calcium excretion.

This may be effected in whole or in part by dietary control and Nordin (1972) has described a low calcium, low oxalate diet as the simplest and most effective regime. Dietary control, however, whilst being an ideal form of management in a metabolic unit poses formidable day to day difficulty to a patient and these difficulties are compounded when circumstances necessitate meals away from home as when travelling and when feeding is institutional. In these circumstances there is the need for an effective agent to reduce the absorption of ingested calcium. Sodium cellulose phosphate is demonstrably effective in this respect and so far has proved innocuous. It is considered that there is a case for its use, suitably monitored, in cases of recurrent urolithiasis who have been shown to absorb calcium excessively from the intestine and to be hypercalciuric.

Summary

Sodium cellulose phosphate can significantly diminish the absorption of calcium from the intestine; there is concomitant diminution of urinary calcium excretion. The plasma levels of the divalent cations do not appear to be influenced by this therapy.

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A Geographical and Historical Survey of the Composition of Urinary Stones

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The problem of urolithiasis is not a simple one for many kinds of stones are known which probably require different conditions for their nucleation and growth. Calculi are found in the kidneys, ureters, bladder and urethra and for those not resulting from any anatomical abnormality, there is no proven reason why growth should occur in say the upper urinary tract as opposed to the lower. Nevertheless, the results of many epidemiological studies (see, for example, references in review articles such as Andersen, 1969) have shown the existence of well-defined zones in the world in which either upper or lower urinary tract stones predominate. Bladder stones in children and adults are a problem in certain areas of technically developing countries like India and Thailand, while kidney stones in adults constitute most of the calculi from industrialised countries. Some possibly indirect connection between these 2 broad categories is, however, likely, for in certain countries of intermediate economic development, both varieties are found, usually but not always in different areas, and the distribution of upper and lower urinary tract stones in them is again dependent on the extent and duration of "industrialisation" present. There is also evidence that bladder stones were a problem in parts of Great Britain, Northern Ireland and Northern Europe prior to this century but they died out about 50 to 60 years ago and have been succeeded by kidney stones. Conditions which have led or are leading to the disappearance of one kind probably then favour the formation of the other.

Stones also differ widely in composition. Many compounds can crystallise in them and frequently several are present in one calculus, but the importance of each constituent, as judged by its frequency of occurrence in collections of stones, varies considerably. In a geographical and historical investigation of the composition of urinary calculi, we have studied representative collections of stones from different countries and found that a few constituents, not always the same, predominate in each but that there is an overall similarity in the total amount of some of the constituents in collections comparable with respect to the variables already mentioned, namely the patient's age, the site of the stone in the urinary tract and the extent of economic development in the geographical area concerned (Sutor, 1972).

We have now extended this work using a computer to group together comparable collections of stones and then to derive data on the patients and the calculi in each subdivision. This we hope will lead to a better understanding of the different types of urolithiasis as revealed by our study of stone composition, and demonstrate their distribution past and present on a geographical basis.

Material and Methods

Collections of urinary calculi from the following countries, cities and institutions are included in this study: Czechoslovakia (99 stones), Eire (69), England (656 stones from 10 cities), India (176 stones from 2 centres), Kuwait (67), Northern Ireland (71), South Africa (52), Scotland (302 stones from 2 centres), Thailand (183), Turkey (306), United States of America (43) and museum collections in England (193). Although we also have stones from Spain, Indonesia and Sudan, these were excluded since data on them and the patients were missing or suspect.

As far as we could ensure, the collections are representative samples of the calculi and patients in the different countries and centres. They are comprised of at least 40 stones from different persons, obtained in sequence as patients presented for operation or treatment in the area concerned. We would have preferred a minimum number of 70 but this was not always possible. As far as we are aware, selection of stones only occurred in the case of 2 museum collections and this was necessary because of the large number of specimens in each. A random selection was sent us from the Norwich Hospital Museum Collection and only whole stones were examined from the Sir Henry Thompson Collection in the Museum of the Royal College of Surgeons, London, because the sequential deposition of compounds could not be determined in those removed by lithotrity.

The crystalline compounds present in the nucleus (if discernible), interior and surface areas of the calculi were determined by the X-ray powder method using techniques described previously (Lonsdale, Sutor and Wooley, 1968*a*; Sutor and Wooley, 1969*b*). Each component present in a stone was weighted according to the amount found in the different layers using the scheme described in the above papers. This weighted composition of the nucleus, interior and surface, and any information on the patients and the stones, were coded and punched on cards (Sutor, Wooley and Illingworth, 1974). Apart from the composition, the only data on the cards relevant to this study are the patient's identification number, country or town of residence, age, sex, the number of stones formed, their total weight and their site in the urinary tract. Programs described in our previous paper (Sutor *et al.*, 1974) were used to select stones according to different variables and to compute the overall composition of such groups, the frequency of occurrence of constituents in them, the combination of compounds in stones of mixed composition, etc.

The variables chosen to select and group the stones were suggested by work in our previous papers. The composition of several collections in this survey has already been published in a series of papers in this *Journal* (Lonsdale *et al.*, 1968*a* and *b*; Sutor and Wooley, 1969*a*, 1970, 1971, 1972). The results have been expressed as firstly, the percentage number of stones containing an observable quantity of a particular compound, and secondly, the weighted percentage amount of each constituent averaged over all the stones in the collection. A comparison of the weighted percentage composition shows there is a similarity among collections comparable with respect to the site of the stone in the urinary tract, the patient's age and the extent of industrialisation present in the area (Sutor, 1972). Thus collections of adult kidney stones from industrialised countries have a fairly similar overall composition with respect to the different constituents, as do collections of children's bladder stones from technically developing countries, but these 2 types differ significantly from each other. Accordingly, the major divisions chosen are adult and children's upper and lower urinary tract stones in industrialised and technically developing countries. Children are taken as being under 21 years of age and the grouping of the countries and collections is based on our preliminary composition studies:

Group I consists of the industrialised countries subdivided into
  Ia Eire, England, Northern Ireland, Scotland, South Africa, United States of America.
  Ib Czechoslovakia, Kuwait.
Group II consists of the technically developing countries
  India, Thailand, Turkey.
Group III consists of museum collections.

Results

Data for the Patients and the Stones

The number of stone cases from each country and the total for each subdivision are listed in Table I. Because of the method used in assembling collections, the figures give no information on the relative stone incidence in the various countries or in the different subdivisions.

Data for the stones and patients are found in Table II. Adults with lower urinary tract calculi are significantly older than those with upper tract ones, but this is not the case for the children. Adult patients with upper urinary tract stones in Group Ia are significantly older ($P<0{\cdot}001$) than those in Groups Ib and II, but there is no significant difference in age between those in the last 2 groups. Adults with lower urinary tract stones in Group Ia are significantly older than those in Groups II and III ($P<0{\cdot}001$ and $P<0{\cdot}05$) and the Group III stone formers are older than the Group II ($P<0{\cdot}001$). Children with lower urinary tract stones in Group II are significantly younger than those in Groups Ia and III ($P<0{\cdot}001$). Children with upper urinary tract stones in Group II are also significantly younger than those in Group Ia ($P<0{\cdot}05$).

Table I

Number of Adult and Children's Upper and Lower Urinary Tract Stones from the Different Countries Divided into the 3 Groups (see text)

		Adults		Children	
Group	Country	Upper Tract Stones	Lower Tract Stones	Upper Tract Stones	Lower Tract Stones
Ia	Eire	42	18	6	1
	England	400	78	48	13
	Northern Ireland	59	7	3	...
	Scotland	200	80	11	3
	South Africa	44	3	3	...
	United States	16	...	...	...
	Total	761	186	71	17
Ib	Czechoslovakia	96	1	1	...
	Kuwait	64	2	1	...
	Total	160	3*	2*	...
II	India	31	38	16	86
	Thailand	105	19	...	58
	Turkey	29	6	123	88
	Total	165	63	139	232
III	Museum Collections	...	115	...	70

* Number of stones in group too small to be included in calculations.

The number of males always exceeds the number of females, but a higher proportion of upper urinary tract stone formers compared with the lower tract ones is female for both adults and children, but excluding the children's bladder stones of Group Ia where the numbers involved are too small for the difference to be significant.

Lower urinary tract stones whether from adults or children have a greater average weight than upper urinary tract calculi and, as probably expected, specimens in museum collections tend to be the heaviest ones.

In all groups single stones predominate over multiple.

Composition of the Stones

In the different groups of adult and children's upper and lower urinary tract stones in industrialised and developing countries and in museum collections, between 4% and 45% of the calculi are of

Table II

Data for the Patients and Stones in the 3 Groups

	Adults		Children	
Group	Upper Tract Stones	Lower Tract Stones	Upper Tract Stones	Lower Tract Stones
(a) Average age and standard error				
Ia	44·9±0·5	61·7±1·0	9·8±0·8	9·4±1·5
Ib	39·6±0·9	...	...	...
II	38·5±1·5	46·2±2·0	7·9±0·4	5·3±0·2
III	...	57·5±1·5	...	8·6±0·6
(b) Number of males to females				
Ia	454 : 293	151 : 27	40 : 30	8 : 7
Ib	106 : 54	...	...	...
II	55 : 19	62 : 1	105 : 34	208 : 22
III	...	96 : 14	...	56 : 1
(c) Average weight (g) of stone(s) formed and standard error				
Ia	2·24±0·23	9·90±1·58	0·98±0·21	4·35±0·95
Ib	0·93±0·15	...	...	...
II	2·35±0·29	15·66±2·81	1·43±0·14	4·68±0·69
III	...	29·13±4·16	...	14·71±1·78
(d) Average number of stones formed and standard error				
Ia	1·62±0·18	5·73±1·45	1·48±0·15	1·20±0·15
Ib	1·72±0·36	...	...	...
II	2·09±0·41	1·27±0·18	1·58±0·13	1·06±0·02
III	...	1·60±0·49	...	1·05±0·03

pure composition, *i.e.* they consist of a single crystalline substance or of different forms or hydrates of a compound such as the two hydrates of calcium oxalate. The rest of the stones are of mixed composition.

Three methods have been used to present the composition of the calculi in the different groups. These are the weighted percentage amount and the percentage frequency of occurrence of each constituent which have already been mentioned, and a classification of the stones based on the constituents present. In order to simplify and generalise the last, the different forms or hydrates of a compound have been grouped together under their common name, thus stones consisting of calcium oxalate + calcium phosphate may represent either or both of the calcium oxalates combined with one or several of the calcium phosphates in any proportion. The number of combinations would therefore appear to be large but, in practice, certain constituents predominate in these general groups, and any frequently occurring associations in the general stone composition types encountered are listed in Table IV and discussed below.

Calcium Oxalate + Calcium Phosphate Stones (C + F in Table IV)

There are 411 calculi with this composition of which 405 contain some apatite. However, only hydroxyapatite is present in 316, only carbonate-apatite in 58 and a mixture of both in 31. Of the 316 stones containing only hydroxyapatite, 211 consist of calcium oxalate monohydrate + the dihydrate + hydroxyapatite, 64 of the monohydrate + hydroxyapatite and 16 of the dihydrate + hydroxyapatite. The sequence of constituents is very varied but frequently calcium oxalate and phosphate occur together in all stone areas. The total weighted percentage amounts of each compound are calcium oxalate monohydrate (36%), calcium oxalate dihydrate (26%), carbonate-apatite (8%), hydroxyapatite (26%) and other calcium phosphates (4%). The amount of calcium oxalate dihydrate in relation to the monohydrate and the total quantity present are greater than in any other composition type.

Calcium Phosphate + Struvite Stones (F + G)

These are infection calculi formed in the presence of urea-splitting organisms. Any newberyite present in these and other calculi would result from the decomposition of struvite (Sutor, 1968). Carbonate-apatite + struvite are the sole constituents of 191 of the 244 stones consisting of both calcium phosphate and struvite, they occur with other calcium phosphates in a further 34 and only 19 stones in this general composition type do not have some carbonate-apatite. In calculi consisting of carbonate-apatite + struvite, either constituent can be the minor or major one contributing between 3% and 97% of the total crystalline material, but often roughly equal quantities of each are present, and the average overall amounts are about the same (53% and 47%) with a slight excess of carbonate-apatite. The compounds are not laid down in discrete bands but are intimately mixed generally from nucleus to surface.

Hydroxyapatite occurs in only 28 stones in this group and in 17 of these carbonate-apatite is also a constituent. As well as the apatites, brushite, whitlockite and octacalcium phosphate are present in some calculi. Whereas the last 2 were often mixed with carbonate-apatite and struvite, brushite was only found on the surface of 2 stones possibly started by infection since carbonate-apatite and struvite are the nucleus constituents. The presence of brushite, an acidic salt, would suggest a change in urinary pH, since it would not form in the alkaline condition associated with infection by urea-splitting organisms. The average weighted amounts of the constituents are carbonate-apatite (48%), hydroxyapatite (2%), other calcium phosphates (3%) and struvite (47%).

Calcium Oxalate + Calcium Phosphate + Struvite Stones (C + F + G)

There are 74 calculi having this overall composition. Carbonate-apatite is present in all but 1 and calcium oxalate monohydrate in all but 9. However, calcium oxalate dihydrate and calcium phosphates other than carbonate-apatite can also occur. Thirty-five of the stones were originally pure calcium oxalate, almost invariably calcium oxalate monohydrate, around which is a deposit of varying thickness of carbonate-apatite + struvite, containing in 11 cases a small amount of calcium oxalate. In these examples, probably urinary infection developed subsequent to stone formation. Another 25 stones have nuclei of carbonate-apatite + struvite, but the outer layers consist of these compounds with a small amount of calcium oxalate. Four other stones have interiors of carbonate-apatite + struvite and outer layers of calcium oxalate. Infection was likely to be responsible for the last 2 varieties, but urinary conditions subsequently changed to permit precipitation of calcium oxalate. Sufficient samples could not be obtained to determine the sequence of constituents in the other calculi of this composition. The weighted percentage amounts of each constituent in this type are calcium oxalate monohydrate (23%), calcium oxalate dihydrate (5%), carbonate-apatite (40%), hydroxyapatite (4%), other calcium phosphates (2%) and struvite (26%).

Uric Acid + Calcium Oxalate Stones (A + C)

Anhydrous uric acid + calcium oxalate monohydrate account for 33 of the 73 stones composed of uric acid + calcium oxalate, and this combination of constituents occurs in all but 3 of the 40 remaining calculi. Calcium oxalate dihydrate is present in 22 of these 40 stones, and uric acid dihydrate in 25, but only in 1 instance is it not associated with anhydrous uric acid. The amount of uric acid and calcium oxalate in a stone can account for between 3% and 97% of the crystalline material, and for all stones of this type the total overall quantity of uric acid (55%) is greater than that of calcium oxalate (45%). Individual contributions are anhydrous uric acid (48%), uric acid dihydrate (7%), calcium oxalate monohydrate (38%) and calcium oxalate dihydrate (7%).

Ammonium Acid Urate + Calcium Oxalate Stones (B + C)

There are 206 stones with this composition and both hydrates of calcium oxalate are present in 121, only the monohydrate in 75 and only the dihydrate in 10. Calcium oxalate monohydrate therefore occurs more frequently with ammonium acid urate than does the dihydrate. Although in some stones only small amounts of oxalate or urate may be present, these types of constituents usually occur in roughly equal amounts. The overall weighted percentage amounts of individual constituents in stones of this type are ammonium acid urate (39%), calcium oxalate monohydrate (46%) and calcium oxalate dihydrate (15%).

Uric Acid + Ammonium Acid Urate + Calcium Oxalate Stones (A + B + C)

Anhydrous uric acid + ammonium acid urate + calcium oxalate monohydrate are the sole constituents of 24 of the 66 stones belonging to this composition group, and this combination, with other constituents, occurs in a further 36. Calcium oxalate dihydrate is present in 27 which almost invariably also contain the monohydrate, and uric acid dihydrate occurs in 22 and is associated with the anhydrous compound in all but 3 instances. The 3 main types of constituents occasionally occur together in a particular stone layer, but nearly half the stones have nuclei of only ammonium acid urate+calcium oxalate. The weighted percentage amounts of the constituents are anhydrous uric acid (34%), uric acid dihydrate (6%), ammonium acid urate (26%), calcium oxalate monohydrate (25%) and calcium oxalate dihydrate (9%).

Uric Acid+Ammonium Acid Urate Stones (A+B)

Only 17 stones have this composition and uric acid+ammonium acid urate frequently occur together throughout the stone. The percentage amounts of the constituents are anhydrous uric acid (63%), uric acid dihydrate (14%) and ammonium acid urate (23%).

Ammonium Acid Urate+Calcium Oxalate+Calcium Phosphate+Struvite Stones (B+C+F+G)

Calcium oxalate monohydrate and carbonate-apatite are the most frequently occurring forms of calcium oxalate and calcium phosphate in the 36 stones of this composition. The structure of many of the calculi suggests that they were originally ammonium acid urate+calcium oxalate but that infection probably developed later causing the deposition of struvite and carbonate-apatite. In the others, carbonate-apatite and/or struvite occur(s) with ammonium acid urate and/or calcium oxalate throughout the calculus. The average percentage amounts of each constituent are ammonium acid urate (22%), calcium oxalate monohydrate (29%), calcium oxalate dihydrate (7%), carbonate-apatite (13%), hydroxyapatite (3%) and struvite (26%).

Ammonium Acid Urate+Calcium Oxalate+Struvite Stones (B+C+G)

Calcium oxalate monohydrate is again the more frequently occurring form of oxalate in the 31 calculi of this type. In about half of these, struvite is deposited around a central nucleus of ammonium acid urate+calcium oxalate, and in the others there are mixtures of the 3 main constituents throughout. The struvite may have resulted from urinary infection, but, as in all these calculi of mixed composition, we have not the clinical information to verify that this compound is formed only through the action of urea-splitting organisms. The average percentage of each constituent type is ammonium acid urate (35%), calcium oxalate monohydrate (32%), calcium oxalate dihydrate (8%) and struvite (25%).

Ammonium Acid Urate+Calcium Phosphate+Struvite Stones (B+F+G)

In the industrialised countries, all calculi of this composition investigated probably resulted from a high excretion of uric acid and a urine infected by urea-splitting bacteria, but it is not known whether those from technically developing areas also need similar conditions or whether they can form in non-infected urine. The average amounts of each constituent in the 37 stones in this group are ammonium acid urate (21%), carbonate-apatite (27%), hydroxyapatite (5%) and struvite (47%).

Ammonium Acid Urate+Calcium Oxalate+Calcium Phosphate Stones (B+C+F)

In most of these calculi there is a nucleus of ammonium acid urate+calcium oxalate, and the calcium phosphate is present with these compounds in the outer layers. The overall weighted amounts of material in the 29 stones with this composition are ammonium acid urate (24%), calcium oxalate monohydrate (43%), calcium oxalate dihydrate (16%), carbonate-apatite (8%), hydroxyapatite (7%) and other calcium phosphates (2%).

Ammonium Acid Urate+Struvite Stones (B+G)

The relative amounts of each type of constituent are 42% and 58% respectively. Most of these stones occur in museum collections (Table IV), and we do not know whether urinary infection is a necessary prerequisite for the formation of calculi of this composition.

Uric Acid+Calcium Oxalate+Calcium Phosphate Stones (A+C+F)

There are only 12 calculi with this composition and in them, there can be areas consisting of calcium oxalate monohydrate+anhydrous uric acid and of calcium oxalate monohydrate+calcium phosphate (usually hydroxyapatite), and sometimes a small sample contained all 3 types of constituents. The relative amounts are anhydrous uric acid (22%), uric acid dihydrate (7%), calcium oxalate monohydrate (46%), calcium oxalate dihydrate (13%), carbonate-apatite (3%), hydroxyapatite (8%) and other calcium phosphates (1%).

Stones Containing Sodium Acid Urate Monohydrate ($J+C$ and $B+J+C$)

This compound was found with either of the calcium oxalates (more frequently with the monohydrate), and also with calcium oxalate+ammonium acid urate, but we have not yet encountered a mixture of just the 2 urates.

Composition of the Groups

Adult Upper Urinary Tract Stones

Group Ia. The most abundant and frequently occurring constituents are calcium oxalate monohydrate, calcium oxalate dihydrate and the apatites (Table III). The calcium oxalates contribute

Table III

Weighted Percentage Composition and, in italics, Percentage Occurrence of the Constituents in Adult and Children's Upper and Lower Urinary Tract Stones in the 3 Groups

Group and No. of Stones	Constituents															
	A1	A2	B	J	C1	C2	D	E	F1	F2	F3	F4	F5	G1	G2	H
(*a*) Adult upper urinary tract stones																
Ia 761	1	>0	>0	...	30	25	1	...	17	13	1	1	>0	...	9	1
	2	*1*	*1*	*>0*	*68*	*54*	*1*	...	*33*	*38*	*2*	*5*	*1*	*1*	*22*	*3*
Ib 160	18	1	2	...	40	22	1	...	6	4	...	>0	...	...	6	...
	29	*7*	*9*	*1*	*78*	*52*	*1*	...	*14*	*23*	*1*	*2*	*1*	...	*13*	*1*
II 165	4	...	3	1	46	10	...	...	13	6	...	2	...	2	11	2
	10	*1*	*12*	*3*	*79*	*31*	...	...	*34*	*26*	...	*7*	*1*	*8*	*24*	*7*
(*b*) Adult lower urinary tract stones																
Ia 186	3	2	2	...	21	11	1	...	24	11	2	2	1	>0	19	>0
	6	*3*	*11*	*1*	*49*	*33*	*1*	...	*50*	*31*	*5*	*7*	*7*	*2*	*44*	*2*
II 63	18	1	10	...	37	17	...	...	4	3	1	>0	...	...	8	1
	37	*8*	*44*	*3*	*79*	*55*	...	...	*27*	*13*	*3*	*2*	...	...	*27*	*5*
III 115	28	11	11	...	15	1	4	...	10	3	...	...	...	3	12	2
	62	*41*	*56*	...	*55*	*10*	*4*	...	*34*	*18*	*1*	*3*	...	*24*	*46*	*11*
(*c*) Children's upper urinary tract stones																
Ia 71	>0	...	>0	...	15	17	6	...	33	3	...	3	>0	>0	22	1
	1	...	*3*	...	*31*	*30*	*6*	...	*59*	*13*	...	*11*	*1*	*3*	*55*	*6*
II 139	1	>0	24	2	46	12	1	1	4	1	...	1	...	>0	7	>0
	4	*1*	*68*	*5*	*86*	*40*	*1*	*1*	*17*	*8*	...	*4*	...	*1*	*16*	*2*
(*d*) Children's lower urinary tract stones																
Ia 17	4	1	3	...	4	7	4	...	29	3	8	4	7	...	21	5
	6	*6*	*18*	...	*18*	*12*	*6*	...	*71*	*18*	*24*	*18*	*29*	...	*59*	*18*
II 232	6	1	34	1	34	16	...	1	1	1	...	...	...	...	5	>0
	19	*9*	*91*	*4*	*91*	*70*	...	*1*	*9*	*5*	*1*	>0	...	*>0*	*21*	*>0*
III 70	18	2	25	...	34	5	1	...	3	2	1	...	...	5	4	>0
	46	*11*	*76*	*1*	*80*	*29*	*1*	...	*23*	*14*	*7*	...	*1*	*27*	*24*	*3*

Key: A1 = anhydrous uric acid, A2 = uric acid dihydrate, B = ammonium acid urate, J = sodium acid urate monohydrate, C1 = calcium oxalate monohydrate, C2 = calcium oxalate dihydrate, D = *l*-cystine, E = xanthine, F1 = carbonate-apatite, F2 = hydroxyapatite, F3 = brushite, F4 = whitlockite, F5 = octacalcium phosphate, G1 = newberyite, G2 = struvite, H = unidentified material.

55% of the total crystalline material in the group and the calcium phosphates, 32%. Although more stones contain hydroxyapatite than carbonate-apatite, the weighted percentage amount of hydroxyapatite is less than that of carbonate-apatite. Table IV which classifies the stones according to the compounds present, shows that the most important composition types consist of calcium oxalate+calcium phosphate (36% of the calculi), pure calcium oxalate (31%) and calcium

Table IV

Percentage Number of Stones Classified According to the Compounds Present for the Different Groups of Adult and Children's Upper and Lower Urinary Tract Calculi

In order to simplify this table only those stones consisting of a combination of constituents which contribute 3% or more to one of the groups (12% or more for the small collection of 17 stones) are included. To differentiate the presence or absence of stones of a particular composition, the following nomenclature has been adopted:
* Some stones of this composition but they constitute less than 3% of the total number in the group.
... No stones of this composition in the group.

	Percentage Number of Stones of a Particular Composition in Each Group										
	Adult Upper Tract Stones in Group			Adult Lower Tract Stones in Group			Children's Upper Tract Stones in Group		Children's Lower Tract Stones in Group		
Stone Composition	Ia	Ib	II	Ia	II	III	Ia	II	Ia	II	III
C+F	36	20	19	26	13	*	10	4	*	*	*
C	31	35	31	14	16	*	21	13	*	4	3
F+G	16	6	11	21	3	9	49	*	29	*	...
F	6	...	4	10	...	*	3	*	18	...	...
C+F+G	4	4	5	10	6	4	*	3	...	...	*
A	*	9	...	*	*	7	...	...	...	...	4
A+C	*	13	6	*	13	10	*	*	*	*	7
B+C	*	*	*	...	6	*	...	51	...	49	11
A+B+C	*	*	*	*	10	6	...	*	...	14	17
A+B	*	*	...	*	...	7	...	...	...	...	4
B+C+F+G	*	*	*	...	3	4	...	*	...	6	16
B+C+G	...	...	...	...	3	...	*	*	...	9	6
B+F+G	*	*	*	6	*	7	...	6	12	*	...
B+C+F	...	...	5	...	3	...	*	3	...	4	4
B+G	...	...	...	*	*	*	...	...	...	*	4
F+G+H	*	...	*	*	...	*	4	...	12	...	*
A+C+F	*	*	...	...	3	...	...	...	...	...	...
D	*	*	...	*	...	3	6	*	...	...	*
J+C	*	...	*	...	...	...	...	3	...	...	...
B+J+C	...	...	*	...	...	...	...	*	...	3	...
A+B+G	...	...	...	...	*	3	...	...	...	...	...
A+B+C+G	...	...	...	*	*	8	...	...	...	*	3
A+B+C+F+G	...	...	*	...	...	8	...	...	...	*	6
Other combinations including contributions from types marked *	7	13	19	13	21	24	7	17	29	11	15
Total number of stones in each group	761	160	165	186	63	115	71	139	17	232	70

Key to stone constituents: A = either or both of the uric acids, B = ammonium acid urate, J = sodium acid urate monohydrate, C = either or both of the calcium oxalates, F = one or more of the calcium phosphates (carbonate-apatite, hydroxyapatite, brushite, whitlockite, octacalcium phosphate), G = struvite and/or newberyite, H = unidentified material.

phosphate + struvite (16%). The last variety is often referred to as carbonate-apatite + struvite since these are the constituents usually present. The whole group is dominated by the collections from Great Britain and Ireland, and in these countries the calcium oxalate + calcium phosphate stones predominate over the pure calcium oxalate ones. For the very small number of stones from South Africa (44) and United States of America (16) belonging in this particular group, the reverse is, however, true.

Group Ib. The 2 hydrates of calcium oxalate are again the most important constituents and together account for 62% of the crystalline material in this group (Table III). Anhydrous uric acid contributes 18% and the calcium phosphates only 10% to the weighted percentage composition. The most important composition type is the pure oxalate stone which accounts for 35% of the calculi (Table IV). In spite of the excess of uric acid over calcium phosphate, the calcium oxalate + calcium phosphate variety is next (20%) followed by stones composed of uric acid + calcium oxalate (13%) and pure uric acid (9%).

Group II. Calcium oxalate monohydrate is again the most important constituent, then carbonate-apatite, struvite, calcium oxalate dihydrate and hydroxyapatite, though the frequency of occurrence of the last 3 constituents is not in the same order as the weighted percentage composition (Table III). The calcium oxalates contribute 56% of the crystalline constituents and the calcium phosphates 21%. The most important types of stones are composed of pure calcium oxalate (31%), calcium oxalate + calcium phosphate (19%), calcium phosphate + struvite (11%) and uric acid + calcium oxalate (6%) (Table IV).

Adult Lower Urinary Tract Stones

Group Ia. Carbonate-apatite, calcium oxalate monohydrate and struvite are the most abundant and frequently occurring constituents (Table III) and the total amount of calcium phosphate (40%) exceeds that of calcium oxalate (32%). The most important stone type for the classification in Table IV is that composed of calcium oxalate + calcium phosphate (26% of the calculi), but this is closely followed by infection stones of carbonate-apatite + struvite (21%). If to these one adds the ammonium acid urate + carbonate-apatite + struvite calculi (6%) which also form in certain urine infected by urea-splitting organisms, stones produced under these conditions make up the largest number in the group. Pure calcium oxalate stones now occupying third place are still an important variety (14%) and there are quite a few pure calcium phosphate calculi (10%). This group is also dominated by the collections from Great Britain and Ireland.

Group II. Calcium oxalate monohydrate, anhydrous uric acid, calcium oxalate dihydrate and ammonium acid urate are the most abundant compounds but the frequency of occurrence of the last 2 exceeds that of anhydrous uric acid (Table III). There are no particular composition types accounting for most of the calculi in this group as in the case of upper urinary tract stones (Table IV). Pure oxalate stones, the most common variety, make up only 16% of the total number, while those composed of uric acid + calcium oxalate and calcium oxalate + calcium phosphate both contribute 13%. A large number of stones contain uric acid and/or ammonium acid urate with calcium oxalate. The combination of ammonium acid urate + calcium oxalate is typical of children's bladder stones from technically developing countries (see later) and calculi having both these constituents may have begun in childhood or some adults may also form stones of this composition. Most of the specimens containing uric acid came from India, but those with some ammonium acid urate were evenly distributed among the countries belonging to this group.

Group III. Anhydrous uric acid is the most important constituent followed by calcium oxalate monohydrate, struvite, ammonium acid urate, uric acid dihydrate and carbonate-apatite, and there is very little difference in the amounts of these last 5 compounds (Table III). In this group no particular composition type is outstanding and many stones are of complex composition possibly because they would remain *in vivo* longer than modern ones (Table IV). Stones composed of uric acid + calcium oxalate are the most common type (10% of the total) and many others contain or consist of these constituents with ammonium acid urate (28%). The combination of calcium oxalate + ammonium acid urate without uric acid is found in a few calculi (6%). Rather surprisingly, the number of pure calcium oxalate stones is negligible.

Children's Upper Urinary Tract Stones

Group Ia. Carbonate-apatite and struvite are the dominant constituents followed by the two hydrates of calcium oxalate (Table III). Infection stones account for about half the calculi, pure oxalate ones contribute 21% and the calcium oxalate + calcium phosphate variety makes up 10% (Table IV).

Group II. In this group calcium oxalate monohydrate, ammonium acid urate and calcium oxalate dihydrate are the most important constituents (Table III), 51% of the stones are composed of ammonium acid urate + calcium oxalate (Table IV), and this combination of constituents is present in a further 11%. Pure calcium oxalate calculi are the second most frequent variety, accounting for 13% of the total. Only 4% of the stones are composed of calcium oxalate + calcium phosphate.

Children's Lower Urinary Tract Stones

Group Ia. The small number of stones in this group (17) precludes the possibility of drawing firm conclusions concerning the major constituents and stone types. However, the trend shown indicates that infection stones are likely to be an important variety.

Group II. The major constituents, ammonium acid urate and calcium oxalate monohydrate are present in 91% of the calculi and calcium oxalate dihydrate was found in 70% (Table III). Not unexpectedly, 49% of the stones consist of ammonium acid urate + calcium oxalate (Table IV), and this combination of constituents is present in a further 40%. Stones composed of pure calcium oxalate or calcium oxalate + calcium phosphate are relatively unimportant.

Group III. Calcium oxalate monohydrate, ammonium acid urate and anhydrous uric acid are the most abundant and frequently occurring constituents (Table III), and stones composed of uric acid + ammonium acid urate + calcium oxalate are the most common variety. They account, however, for only 17% of the total number but this combination of constituents is found in another 9% (Table IV). As in the case of adult stones from museum collections, the overall stone composition is often complex in that a large number of compounds are present, and no particular composition type dominates the group. However, a combination of ammonium acid urate + calcium oxalate which accounts for 11% of the stones is also found with other constituents in a further 26%, excluding the ones mentioned above which also contain uric acid. 16% of the stones in this group are composed of ammonium acid urate + calcium oxalate with outer layers of struvite + carbonate-apatite showing that infection occurred subsequent to stone formation. Thus ammonium acid urate + calcium oxalate stones probably originally accounted for 27% of this group and would therefore be the most important type.

Composition of the Nucleus Compared with the Rest of the Stone

Table V compares the weighted percentage composition of the nucleus, or the interior when these areas are homogeneous, with that of the rest of the stone, for the different groups of adult and children's upper and lower urinary tract calculi in industrialised and developing countries and in museum collections. Many stones, in particular some modern upper urinary tract ones, are small aggregates of crystalline material which could not be separated into distinct areas and which had to be sampled as a whole. These calculi were excluded from the calculations, and only in a few instances are the figures representative of the nucleus composition of all the stones in the group. A direct comparison of these figures is therefore not possible, but a comparison of the composition of stone regions within a group shows any differences in the occurrence of constituents in these areas.

Table V

Weighted Percentage Composition of Nucleus and of Rest of Stone for Calculi with Observable Nuclei or with Homogeneous Nuclear and Interior Regions. Stones are Subdivided into Adult and Children's Upper and Lower Urinary Tract Varieties for the 3 Groups

Group and No. of Stones	Stone Area	Constituents															
		A1	A2	B	J	C1	C2	D	E	F1	F2	F3	F4	F5	G1	G2	H
(*a*) Adult upper urinary tract stones																	
Ia 468	Nucleus	1	>0	1	>0	29	10	2	...	24	15	1	2	>0	...	14	>0
	Rest	1	>0	>0	...	20	23	2	...	25	12	1	2	>0	>0	13	>0
Ib 108	Nucleus	17	>0	2	...	47	16	...	...	5	5	...	1	...	...	7	...
	Rest	17	1	3	1	38	24	1	...	6	4	>0	>0	>0	...	4	>0
II 101	Nucleus	6	>0	5	1	46	10	...	...	8	7	...	2	>0	1	12	2
	Rest	7	>0	2	...	45	14	...	...	12	8	...	2	>0	2	7	1
(*b*) Adult lower urinary tract stones																	
Ia 140	Nucleus	2	2	3	>0	27	6	1	...	21	11	2	3	1	...	19	2
	Rest	4	1	2	>0	19	14	1	...	24	10	3	1	2	>0	19	...
II 63	Nucleus	21	>0	11	>0	39	11	...	...	4	2	>0	1	...	...	9	2
	Rest	18	2	9	>0	33	20	...	...	4	3	1	...	...	...	9	1
III 106	Nucleus	29	16	10	...	21	>0	3	...	7	3	...	>0	...	1	7	3
	Rest	28	8	11	...	14	1	3	...	13	4	>0	>0	...	3	14	1
(*c*) Children's upper urinary tract stones																	
Ia 51	Nucleus	>0	...	1	...	15	8	4	...	38	>0	...	3	1	>0	29	1
	Rest	>0	...	...	...	10	12	4	...	45	2	...	2	...	1	23	1
II 107	Nucleus	2	...	37	1	40	9	1	...	3	1	...	1	...	...	5	>0
	Rest	1	>0	13	1	57	15	1	...	4	1	...	1	...	>0	6	>0
(*d*) Children's lower urinary tract stones																	
Ia 17	Nucleus	6	...	4	...	5	5	6	...	29	1	3	5	3	...	24	9
	Rest	3	2	1	...	1	9	3	...	31	4	10	2	11	...	19	4
II 216	Nucleus	4	>0	48	1	31	11	...	1	1	>0	...	>0	...	...	2	...
	Rest	8	2	25	1	34	18	...	1	2	1	>0	...	...	...	8	>0
III 65	Nucleus	12	1	44	...	35	2	...	...	>0	2	>0	...	...	1	1	2
	Rest	22	2	16	>0	34	7	...	...	4	1	1	...	>0	8	5	...

(See Table III for key to symbols)

Calcium oxalate monohydrate is found in greater amounts in the nucleus than in the rest of the stone except in the case of children's upper and lower urinary tract calculi from technically developing countries where the reverse is true. Ammonium acid urate is also a more important constituent of the nucleus for most groups including the aforementioned children's ones. As the children's stones from technically developing countries consist predominantly of a mixture of these 2 compounds, both are unlikely to occur in greater amounts in the nucleus. Since ammonium acid urate is the compound which occurs more abundantly in the nucleus than in the outer area, and the total amount present in the nucleus exceeds that of calcium oxalate monohydrate for the children's lower urinary tract stones, this compound is apparently the more important one in the nucleation of calculi of this composition. Calcium oxalate dihydrate and carbonate-apatite are found in greater amounts in the outer area of stones. The occurrence of struvite, hydroxyapatite and anhydrous uric acid varies from one collection to another and is likely to be dependent on the composition of the stones which predominate in each subdivision. Of the minor constituents brushite, octacalcium phosphate and newberyite are usually found in slightly greater amounts in the outer areas, and whitlockite is probably more important as a nucleus constituent while cystine and sodium acid urate are usually deposited evenly throughout the stone. The occurrence of uric acid dihydrate is variable but, in the one group in which it is a major constituent, it occurs more abundantly in the nucleus.

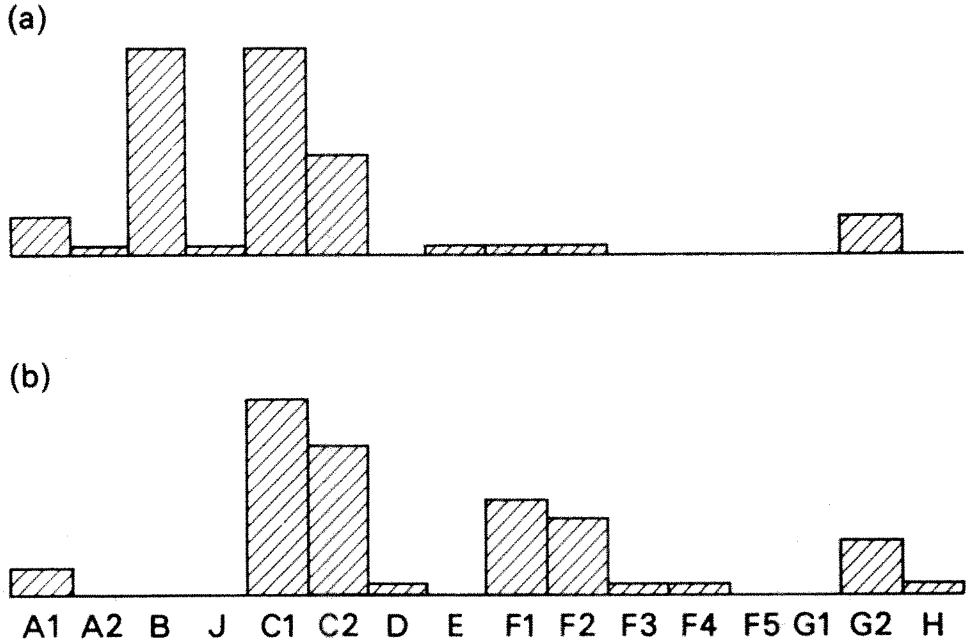
Discussion

Collections of adult upper urinary tract stones which came from industrialised countries and "westernised" areas of technically developing ones possess a fairly similar overall composition. Calcium oxalate monohydrate is the major constituent and this compound, together with the dihydrate, accounts for more than 50% of the crystalline material in each group. The calcium phosphates rank next in Groups Ia and II, and anhydrous uric acid in Group Ib. In Group Ia, the calcium oxalate + calcium phosphate stone occurs more frequently than the pure calcium oxalate one, possibly because of the predominance of this type in Great Britain and Ireland from where most of the stones in this subdivision came. Pure oxalate calculi exceed the mixed oxalate + phosphate ones in the other industrialised countries of Group Ia, in Group Ib and in the technically developing countries. Both are by far the most important types in all groups of adult upper urinary tract stones, but slight regional variations occur in the relative numbers of each. The infection stone consisting usually of carbonate-apatite and struvite is the third most frequent variety in Groups Ia and II but is only fifth in Group Ib. In the last group, stones consisting of uric acid + calcium oxalate and pure uric acid occur more frequently and, though the former type is found in Group II, stones containing uric acid rarely occur in Group Ia.

Adult lower urinary tract stones from industrialised countries contain more calcium phosphate and struvite than the upper tract calculi. About 40% of them consist of pure calcium oxalate or calcium oxalate + calcium phosphate, while 37% contain carbonate-apatite + struvite and probably result from infection by urea-splitting organisms. Adult lower urinary tract stones in technically developing countries and museum collections have a very different composition from those in industrialised countries. They contain large amounts of uric acid and calcium oxalate, and ammonium acid urate is also an important constituent. Combinations of uric acid and/or ammonium acid urate with calcium oxalate are common in both the groups but, whereas pure oxalate stones are an important variety in technically developing countries, they are virtually unknown in museum collections. The same is true for the calcium oxalate + calcium phosphate type.

Children's stones differ in composition from those of adults. Both upper and lower urinary tract calculi from children in technically developing countries contain large amounts of ammonium acid urate and calcium oxalate. Those consisting of or containing these 2 constituents comprise 89% of the lower urinary tract calculi and 62% of upper urinary tract ones. This combination of constituents is also the most common one in children's bladder stones from museum collections, but this group contains much more uric acid than the modern one. A study of the nucleus composition suggests that ammonium acid urate is likely to be more important than calcium oxalate in the nucleation of this type of stone. In the industrialised countries, the most important variety consists of carbonate-apatite + struvite and probably results from infection.

Epidemiological studies mentioned in the introduction indicate that adult and children's bladder stones in technically developing countries and adult upper urinary tract calculi in industrialised areas have the highest incidence, and that, as the standard of living has improved in a country, the former kinds have decreased in number, and in many places vanished, but these changes have been accompanied by an increase in the latter type. Our studies show that a dramatic change in composition has occurred and is occurring as well. This is illustrated in part in the Figure, where the weighted percentage amounts of the individual constituents in children's lower urinary tract stones from technically developing countries are compared with those of adult upper urinary tract calculi from the industrialised countries. (Adult lower urinary tract stones from the former areas are not included since we have not obtained many of these, and some may even be similar to those found in the industrialised countries). The amounts of calcium oxalate, struvite and uric acid in each are roughly the same, the major differences occur in the quantities of ammonium acid urate and calcium phosphate.



Weighted percentage composition of the constituents in (*a*) children's lower urinary tract stones from developing countries and (*b*) adult upper urinary tract stones from industrialised countries. (See Table III for key to the symbols.)

The change in the composition of urinary calculi as countries have become and are becoming industrialised can be summarised as follows. Children's bladder stones from the technically developing areas contain both ammonium acid urate and calcium oxalate, and this is also the most common combination of constituents in the children's bladder stones which occurred in England 70 to 200 years ago. The few adult upper urinary tract stones from technically developing countries and those in museum collections suggest that uric acid and calcium oxalate are the major constituents, and that these compounds frequently occur together. However, adult upper urinary tract stones whether from industrialised countries or from the more "Westernised" areas of technically developing ones, consist predominantly of calcium oxalate + calcium phosphate or pure calcium oxalate. Such composition types are not often found in collections of children's bladder stones, neither does the ammonium acid urate + calcium oxalate variety occur in the industrialised countries. The presence of pure oxalate and calcium oxalate + calcium phosphate types in the group of adult lower urinary tract stones from technically developing countries might indicate a change towards the composition of similar calculi in the industrialised countries.

The other groups in this paper are relatively unimportant, but the fact that they do exist, and a definite composition pattern emerges for them, shows they constitute a problem of their own, if not on the scale of the others. Their composition also emphasises the difference between stones from technically developing and industrialised areas.

Summary

The composition of urinary stones in different countries can be related to the extent of economic development present and the major types of stones in the world, namely children's and adult lower urinary tract calculi in technically developing countries and adult upper urinary tract ones in industrialised areas, are of very different composition.

Approximately 89% of children's stones consist of or contain ammonium acid urate + calcium oxalate and the composition of the nucleus suggests the former compound is more important in the nucleation of such calculi. Of similar composition are children's bladder stones from old museum collections in England.

Large amounts of uric acid and calcium oxalate are present in adult lower urinary tract stones from technically developing countries and museum collections, and many stones contain these 2 compounds frequently with ammonium acid urate.

Adult upper urinary tract calculi from industrialised countries and from "Westernised" areas of technically developing ones, consist predominantly of calcium oxalate + calcium phosphate or pure calcium oxalate. Stones of such composition are not often found in collections of children's bladder calculi, whether from technically developing countries or museum collections, and stones with ammonium acid urate + calcium oxalate do not occur in industrialised countries like Great Britain and America. However, uric acid + calcium oxalate stones, but without ammonium acid urate, are found in some countries in Europe where they are the most frequently occurring type after the pure calcium oxalate and calcium oxalate + calcium phosphate varieties.

Children's stones and adult lower urinary tract ones in industrialised countries and children's upper tract stones in technically developing countries, though of less importance, nevertheless have their own particular composition which again is different for regions of different economic development.

The most frequent combinations of individual constituents in the different composition types are discussed, as well as the sex and average age of the patients and the number and weight of the stones.

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Ureteral and Vesical Metastases in Nephroblastoma

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A case of nephroblastoma with ureteral metastases is described which presented as a large well-differentiated tumour containing a very small non-differentiated polypoid area.

Case Report

A. L., a 6-year-old male child with haematuria was admitted to the Paediatric Clinic of the University of Padova on 14th December 1971. Objective physical examination disclosed a well-developed child. I.V.P. revealed delayed and poor function in the left kidney in which the upper group of calyces were markedly dilated. The right kidney ureter and the bladder presented no abnormality. Preoperative retrograde pyelograms showed a defect in the pelvis of the left kidney (Fig. 1). A simple nephrectomy was then performed.

The deformed kidney measured 8 × 6 × 4 cm and contained a large mass at the lower pole. Renal tissue appeared as a shell of varying thickness, sharply defined from a multilobulated tumour which was characterised by polypoid masses protruding into the renal pelvis (Fig. 2).

Histologically, the rim of the parenchyma, observed at the periphery of the tumour, showed pyelonephritic-like fibrosis and inflammatory infiltrates. The tumour masses protruding into the pelvis were partially cystic. The cysts were lined by low cuboidal or flattened epithelium and separated by thick fibrous septa in which isolated tubules appeared.

The child's postoperative course was uneventful except for a persistent albuminuria. However, 3 months later, the child was readmitted with macroscopic haematuria. Cystoscopy at this time showed a polypoid mass localised on the left ureteral orifice which raised the suspicion of metastases.

The original tumour specimen was retrieved and re-examined histologically by serial sections. While the major part consisted of well-differentiated tissue, re-examination revealed a very small (a few millimetres in diameter) polypoid intrapelvic nodule pushing into the pelvi-ureteric junction. The nodule consisted of fibrillar stroma containing agglomerates of non-differentiated cells (Fig. 3).

Ureterectomy and partial cystectomy were then performed. The ureter showed neoplastic infiltration both at the proximal extremity and in its intravesical tract (Fig. 4). Microscopic findings were the same at the 2 extremities. Both ends of the ureter were partially infiltrated by polypoid masses of mesenchymal tissue in which non-differentiated cells proliferated and tended to form primitive tubular or glomerular embryonal structures, characteristic of Wilms' tumour (Figs. 5 and 6).

The patient was placed on a radio-chemotherapeutic schedule and followed for 1 year. At the time of this report, the child has been readmitted for surgery as a follow-up examination has revealed a retroperitoneal mass diagnosed as metastases of the Wilms' tumour.

Comment

We have described the case of a child where originally a diagnosis of "multilocular renal cyst" (M.R.C.) was made and who subsequently presented vesical metastases. On the basis of this observation the original tumour material was re-examined and a very small circumscribed area of malignant tissue was detected. This experience confirms our opinion that a diagnosis of M.R.C. can be made only after examination of serial section of the specimen. Moreover, we suggest that the presence of a polypoid neoplastic mass in the renal pelvis, no matter how small, predicts a probable subsequent urothelial implant in the lower urinary tract.

While Wilms' tumour usually metastasises via the blood stream and the lymphatics, a few other cases of secondary ureteral implantation have been reported (Mertz, Howell and Heindricks, 1941; Watkins, 1957; Woodhead *et al.*, 1968; Taykurt, 1972). Of these, only Watkins has

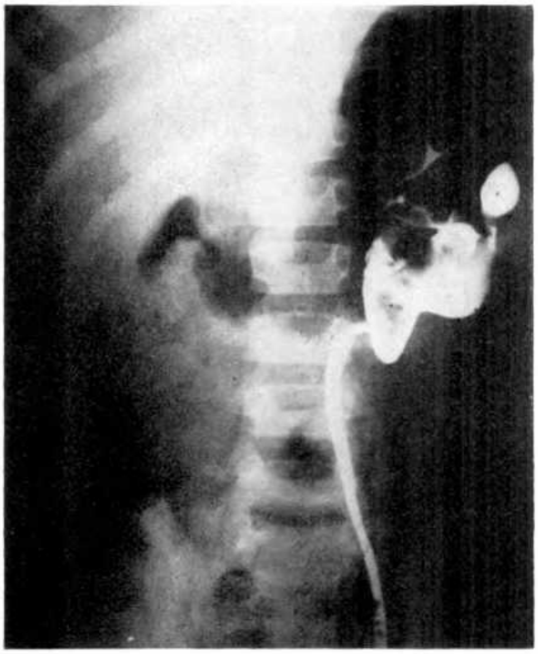

Fig. 1. Retrograde pyelogram demonstrating filling defect in superior calyces and upper part of the pelvis, with marked dilatation of the lower segment of the pelvis.

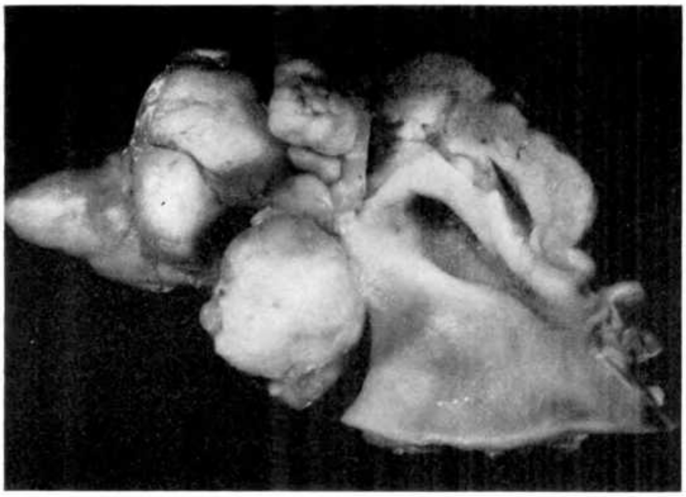

Fig. 2. Kidney showing multilobulated mass protruding into the renal pelvis.

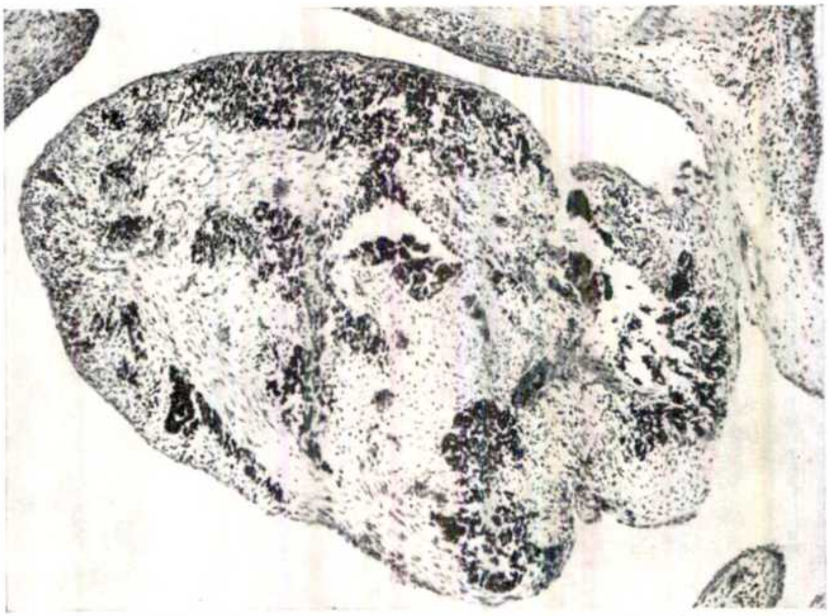

Fig. 3. Small polypoid intracystic nodule with microscopic characteristics of Wilms' tumour. H & E. ×19; ×48.

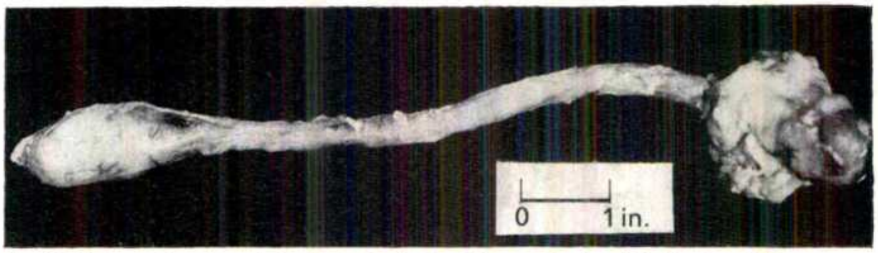

Fig. 4. Ureter with metastatic implantation both at the proximal and distal extremities.

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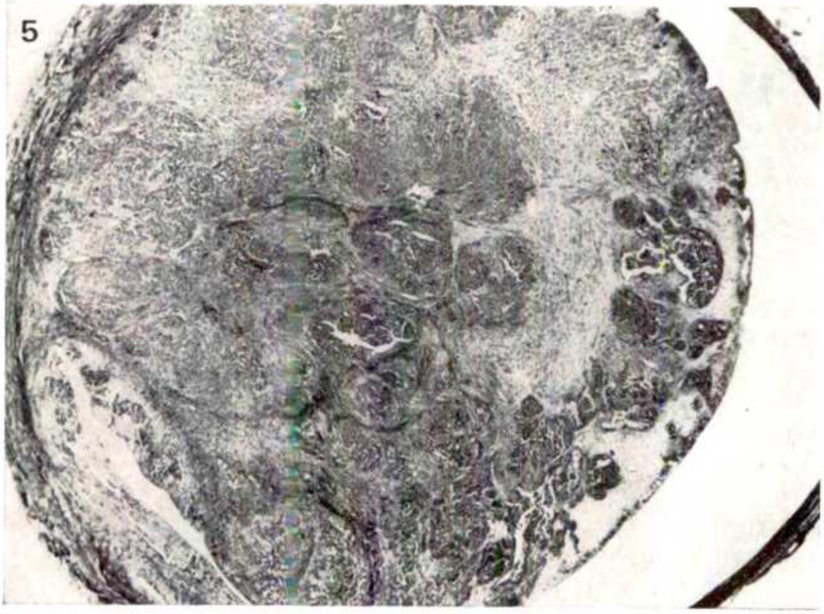

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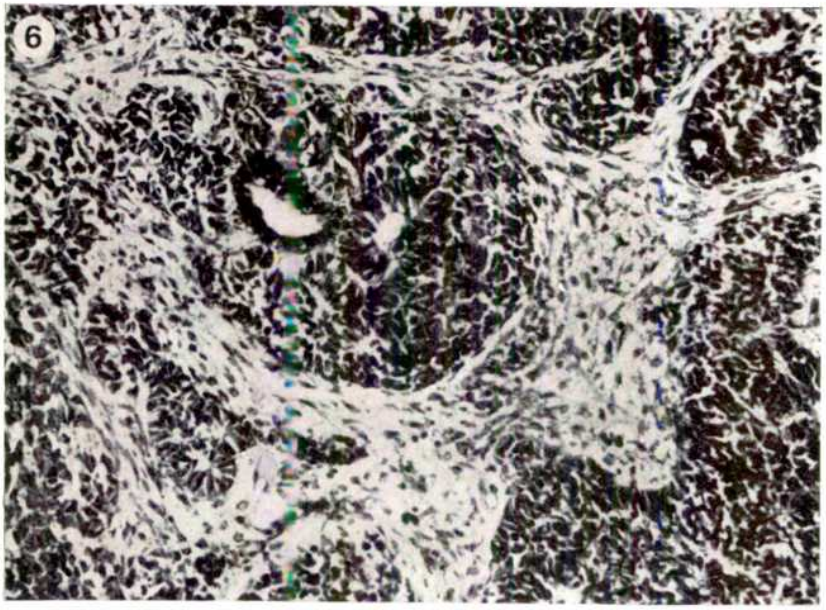

Fig. 5. Histological aspect of neoplastic urothelial implantation at the proximal end of the ureter. H & E. × 12.

Fig. 6. Higher magnification of nephroblastoma infiltrating vesical wall. Note the early differentiation of renal tubules from a mass of undifferentiated cells. H & E. × 150.

described a primary tumour which was found to involve the renal pelvis and extend into the bladder. The rarity of this type of metastasis depends on the fact that Wilms' tumour is usually localised deeply within the renal parenchyma without any direct connection with the pelvis. We believe that there is a causal relationship between nephroblastoma extending into the renal pelvis and urothelial implantation. In this connection Helson and Hajdu (1972), studying the urinary sediment of 15 children with Wilms' tumour, have reported only 2 instances of tumour cell exfoliation. In both these cases there was an extension of nephroblastoma through the renal pelvis. Neoplastic implantation is most likely to occur in the narrower parts of the ureter (e.g. the uretero-vesical junction) in which direct contact with neoplastic cells is prolonged.

On the basis of our experience, we have modified our therapeutic approach to Wilms' tumour. The urine is studied cytologically in all cases. If tumour cells are present in the sediment, we feel justified in suspecting an invasion of the renal pelvis and nephroureterectomy is then performed, using the same procedure employed for epithelial neoplasia of the upper urinary tract. Moreover, if the cytological study is negative, immediately following removal of the kidney, we observe whether the nephroblastoma extends through into the calyces or into the renal pelvis. If this is so the ureter is also excised.

We believe that by resorting to more extensive surgery in suspected cases we can eliminate relapses due to urothelial implantation.

Summary

A case of multilocular renal cyst associated with an intrapelvic small nodule of malignant Wilms' tumour presenting subsequent urothelial metastasis is described. To avoid the possibility of urothelial neoplastic cell implantation the authors suggest more detailed histological examination and removal of the ureter in appropriate cases.

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Total Replacement of Ureter by a Scurasil^{R} Prosthesis in Pigs

Morphology and Renal Function: A Clinical Trial in Two Patients

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During the last decade many attempts have been made to produce an inert synthetic prosthesis for the total replacement of diseased ureters. Various materials have been used: polyethylene, polyvinylchloride, Dacron^{R}, Teflon^{R}, glycol metacrylate gel, hydrophil gel and silicone rubber, but the results have been disappointing. The main problems have been the intolerance of the organism to the foreign materials, obstruction of the prosthesis, urinary leakage, dislodgement of the prosthesis, infection and reflux. Several investigators report hydronephrosis due to aperistalsis of the interposed substitute and subsequent renal failure.

The problems of tissue reaction and tissue incrustations have been partially resolved by using dimethylpolysiloxane (Blum, Skemp and Reiser, 1963). Dislodgement of the prosthesis and reflux have been diminished using a Scurasil^{R} (dimethylpolysiloxane) prosthesis with Rhodergon^{R} (polyethylene glycol terephtalate) cuffs for fixation and an unidirectional valve at the vesical end of the prosthesis (Fig. 1), developed by Auvert, Dufour and associates (Dufour and Auvert, 1971). The preliminary experiments have given promising results.

The present report gives the results of unilateral total ureteral substitution and contralateral nephrectomy in 5 pigs with a follow-up period of 6 to 8 months. This part of the study comprises morphological and kidney function examinations.

Clinical experience is also recorded from treatment of 2 women with bilateral ureteric obstruction, 1 of whom was in anuria.

Material and Methods

The Prosthesis

The prosthesis used was "the latest model" of Rhone-Poulenc's Scurasil^{R} prosthesis with Rhodergon^{R} cuffs for suturing the prosthesis to the regional tissue and an anti-reflux valve at the vesical end. The length of the prosthesis varied from 240 to 300 mm and the diameter from 4·5 to 7·1 mm.

Experimental Animals

Five female pigs of the Danish Landrace breed, 4 to 5 months of age and weighing 44 to 72 kg at the time of surgery were used for the study. The animals were fed during the experimental period with a standard fodder mixture (Gyrd-Hansen, 1968). They were weighed once a week and the daily administration of fodder was calculated on basis of the body weight. Free access to water was permitted.

Anaesthesia

Anaesthesia was induced by intramuscular injection of 2 mg/kg phencyclidinum NFN (Sernylan^{R}) and continued using halothane-oxygen with spontaneous respiration in a semiclosed system (Gyrd-Hansen, 1971). Atropine sulphate was administered intramuscularly.

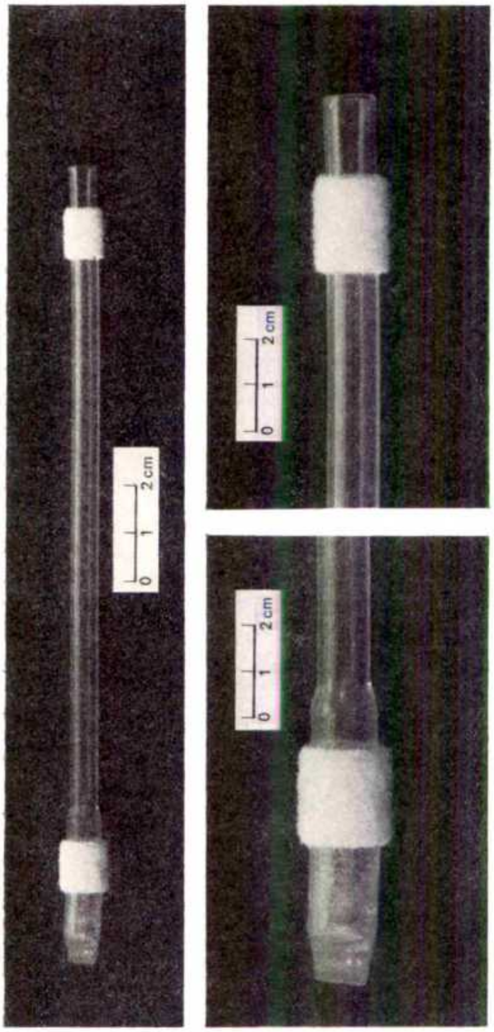

Fig. 1. The prosthesis.

Surgical Procedures

To prevent postoperative ileus and hernia formation a retroperitoneal approach was used (Nerstrøm *et al.*, 1972). A midline incision from the xiphoid process to the pelvic symphysis was made. The parietal peritoneum was freed from the abdominal muscles by blunt dissection and the left kidney and ureter were exposed. The ureter was excised; at the upper end it was cut at, or just above, the uretero-pelvic junction. Through a small peritoneal incision a stall of the bladder wall was extracted and peritoneum was sutured to it with 3-0 Tycron^{R} (polyphile polyester) interrupted sutures. After incision of the bladder the prosthesis was inserted. The bladder wall was fixed to the

Rhodergon^R cuff of the prosthesis with 4-0 Tycron^R interrupted sutures in 2 layers, 1 in the mucosa and 1 in the muscles.

Proximally the prosthesis was inserted into the renal pelvis and the pelvis was sutured to the cuff with 4-0 Tycron^R interrupted sutures in one layer. The peritoneum was then freed from the abdominal wall on the right side and nephrectomy was performed.

Streptocillin^R, 10,000 units per kg per day was given for 3 to 4 days postoperatively.

Postoperative Studies

Blood samples were taken before and 1, 3, 7, 10, 17, 24, 180 and 240 days after surgery for determination of the concentrations in plasma of creatinine, urea, sodium and potassium. The clearances of inulin, endogenous creatinine, urea and para-aminohippuric acid (PAH), the osmolar clearance and the excretion percentages of water, sodium, potassium and chloride were determined 1 and 6 to 8 months after surgery. Each experiment comprised at least 3 periods of 20 minutes. Details of the doses of test substances, the technique and the calculation methods have been published previously (Gyrd-Hansen, 1968). The pigs were killed a few days after the last experiment.

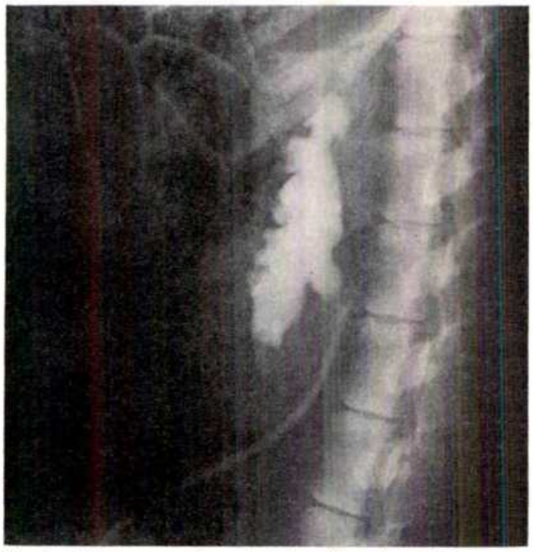

Fig. 2. I.V. urogram 4 weeks after insertion of the prosthesis in pig no. 3.

Intravenous urography was performed 1 month after ureteral replacement using 1 g Urografin^R per kg body weight.

Postmortem Examinations

The animals were killed and bled, and urine for bacteriology was aspirated from the bladder and pelvis, when possible. The kidney, prosthesis and bladder were removed *in toto* and the kidney was weighed. Tissue from the bladder, vesical anastomosis, surroundings of the prosthesis, pelvic anastomosis, renal pelvis and kidney was removed and fixed in phosphate-buffered 10% formalin. Paraffin sections were stained with haematoxylin-eosin and PAS.

Results

The operation was uncomplicated in all cases. No urinary leakage or wound infection was observed. Four pigs urinated 2-6 hours after the operation; in 1 pig (no. 3) urine was not observed until 24 hours postoperatively.

Intravenous urography 4 weeks after ureteral replacement showed normal urograms in all cases with no sign of hydronephrosis (Fig. 2). All pigs had a normal gain of weight, the mean value being 75 kg before operation and 138 kg at the time of sacrifice. 6 to 8 months after ureteral replacement the pigs were taken into the laboratory and here pig no. 6 died from mechanical ileus with intestinal rupture before the last clearance determination was performed.

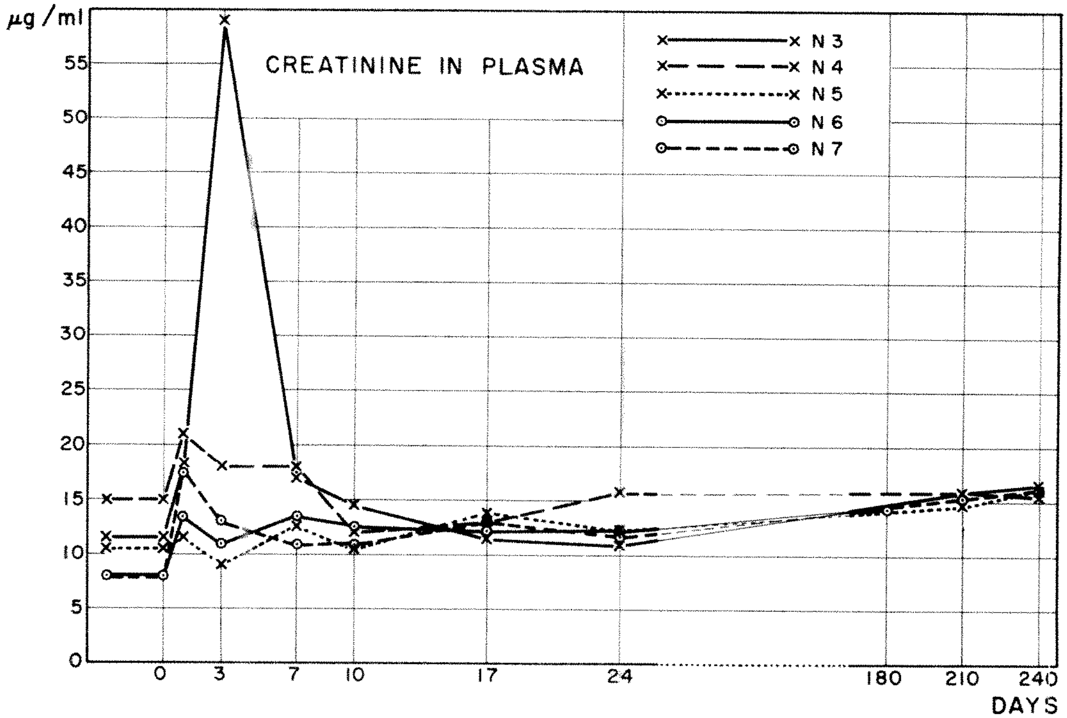

Fig. 3. Plasma creatinine in 5 pigs following unilateral ureter replacement and contralateral nephrectomy.

Kidney Function

Figures 3 and 4 show the concentrations of creatinine and urea in plasma (ug/ml) in the 5 pigs during the observation period. The concentrations of sodium and potassium were constant throughout the observation period. The mean values and standard deviation were 141 ± 2 and 5·4 ± 0·7, respectively. The mean values of the clearances for 5 pigs 1 month after ureteral replacement were at a urine flow of 1·7 ± 0·2 ml/min: C_{In}: 20 ± 1·5, C_{creat}: 21 ± 2·5, C_{urea}: 20 ± 0·8, C_{PAH}: 76 ± 8·1 and the osmolar clearance: 0·55 ± 0·03 ml/min/10 kg b. wt. 6 to 8 months after surgery the mean values were for 4 pigs at a urine flow of 2·6 ± 0·2 ml/min: C_{In}: 17 ± 2·9, C_{creat}: 18 ± 0·6, C_{urea}: 11 ± 1·5, C_{PAH}: 64 ± 7·0 and osmolar clearance: 0·48 ± 0·08 ml/min/10 kg b. wt. The excretion percentages of water, sodium, potassium and chloride were within normal limits and remained normal.

Postmortem Examination

Macroscopic Findings

The prostheses were entirely surrounded by a thin and movable fibrous membrane. Adhesions were found surrounding both anastomoses. The vesical anastomosis and a section (2½ cm) of the prosthesis from pig no. 7 was surrounded by bone tissue. A little distally to the pelvic anastomosis in pigs no. 4 and 5 a small focus of bone tissue lying close to the prosthesis was found.

The bladders were without macroscopic changes except in pigs no. 3 and 4, where the mucosa was slightly thickened and a little rough on the surface. Both in the bladder and in the pelvis the mucosa was found to be slightly reddish, thickened and rough on the surface at the level of the free end of the prosthesis.

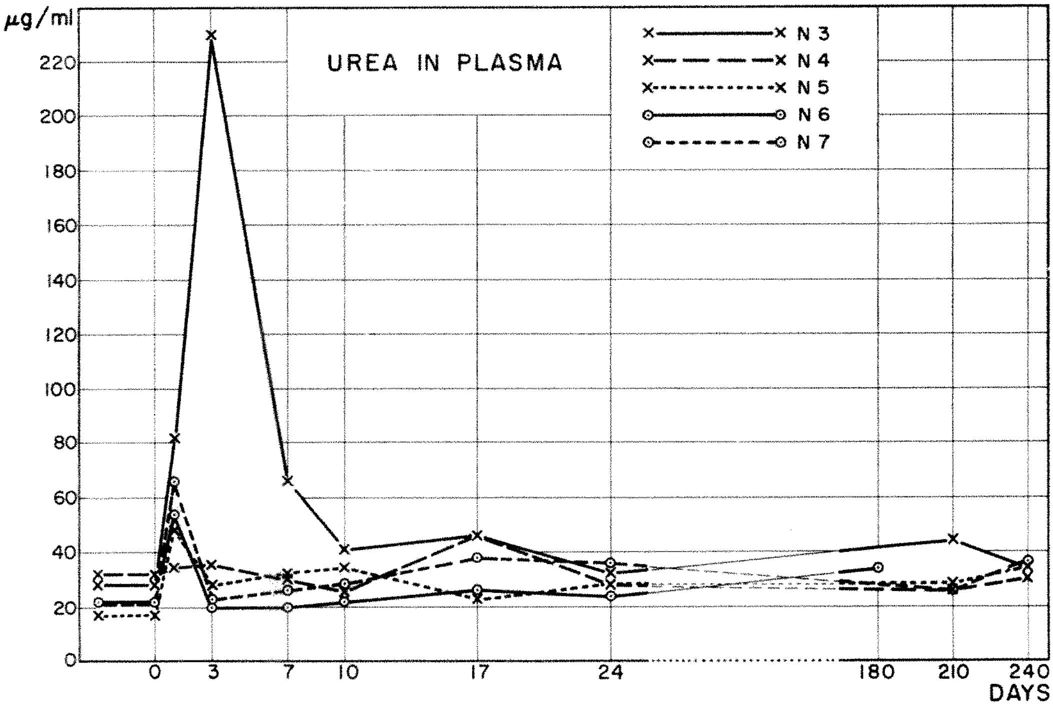

Fig. 4. Plasma urea in 5 pigs following unilateral ureter replacement and contralateral nephrectomy.

The great majority of the anastomoses had healed well with a marked ingrowth of fibrous tissue into the Rhodergon^{R} cuffs (Fig. 5). One of the anastomoses had loosened in 3 pigs; 1 at the pelvic end and 2 at the vesical end, because the sutures had ruptured. Since the fibrous membrane formed a tight seal along the full length of the prosthesis its function was not impaired by the loosening at the anastomosis.

The prostheses from pigs no. 3 and 4 were discoloured and had, on the inside, a thin coat of brownish proteinaceous material without incrustations. Except for a brownish discoloration of the free end in the bladder, the prostheses from the other pigs were clean. The renal pelvis in pig no. 6 was slightly dilated, while the pelvic mucosa from pig no. 3 was slightly rough and coated with a mucous fluid.

The kidneys were enlarged and the parenchyma was slightly firm. They were otherwise without pathological changes.

Urine for cultivation was obtained in 3 pigs only. Urine from pigs no. 3 and 4 showed significant growth of *E. coli*, while urine from pig no. 7 was sterile.

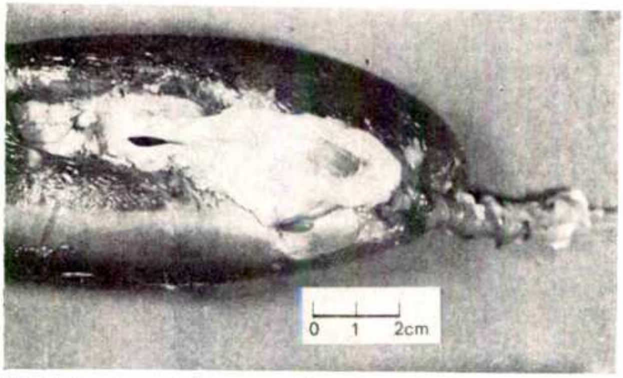

Fig. 5. Anastomosis between pelvis and prosthesis at necropsy in pig no. 5 showing perfect healing.

Microscopic Findings

The bladders were normal except in pigs no. 3 and 4 where accumulations of lymphocytic cells were found just beneath the urothelium. In several places the lymphocytes also infiltrated the urothelium (cystitis follicularis).

Some characteristic changes of the vesical mucosa were seen around the anastomosis. At the level of the free end of the prosthesis the urothelium was higher than normal due to vesiculation and ballooning of the cells (Fig. 6). Close to the entrance of the prosthesis there was squamous metaplasia of the urothelium (Fig. 7) and at the entrance small cysts lined by attenuated urothelium on the inside were found in the lamina propria, which in addition was infiltrated by lymphocytes and macrophages. Around the cuff, both at the healed and loosened anastomoses, the urothelium was missing. In the healed anastomoses the meshes of the cuff were penetrated by scar tissue containing irregular foreign body giant cells. Similar foreign body giant cells were seen around the sutures. The scar tissue around the healed anastomoses was infiltrated by lymphocytes, macrophages and eosinophilic leucocytes. In the scar tissue around the loosened anastomoses aggregations of lymphocytes, foreign body giant cells, small calcifications, and neutrophilic leucocytes were seen, too. The same microscopic changes were seen in the fibrous membrane around the prosthesis. In this membrane the infiltrations with macrophages along the prosthesis was so marked that it gave an impression of a continuous epithelial lining (Fig. 8). Cellular debris and small calcifications were found between the fibrous membrane and the prosthesis. The histological findings at the pelvic anastomosis were essentially like those at the vesical anastomosis. The kidneys were without pathological changes except for compensatory hyperplasia due to unilateral nephrectomy.

The promising results of these experimental studies led us to introduce a clinical trial of the prosthesis, which we have used so far in 2 cases.

Case Histories

Case 1. A 68-year-old woman had been treated in 1962 by radiotherapy for carcinoma of the cervix. Recently she had developed loin pain and an excretion urogram showed bilateral hydronephrosis, worse on the left. The blood urea and serum creatinine were highly elevated. A diagnosis of retroperitoneal fibrosis was made and at laparotomy the frozen section showed non-specific inflammatory changes and fibrosis. The right ureter was mobilised but the left could not be freed intact and was excised; a Scurasil ureter prosthesis was inserted and fixed retroperitoneally. The patient had an uneventful postoperative course. Excretion urogram at 8 days, 2 months, 7 months and 15

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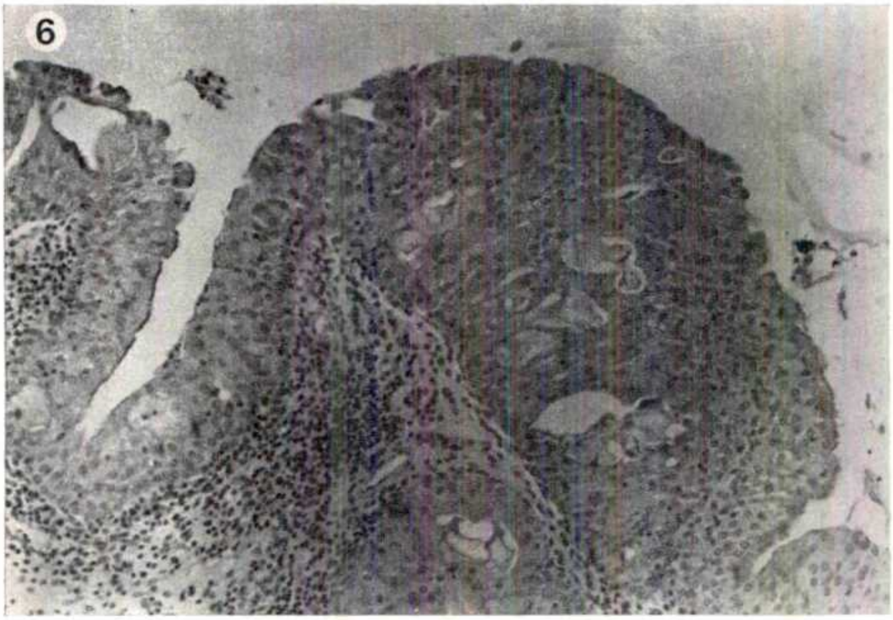

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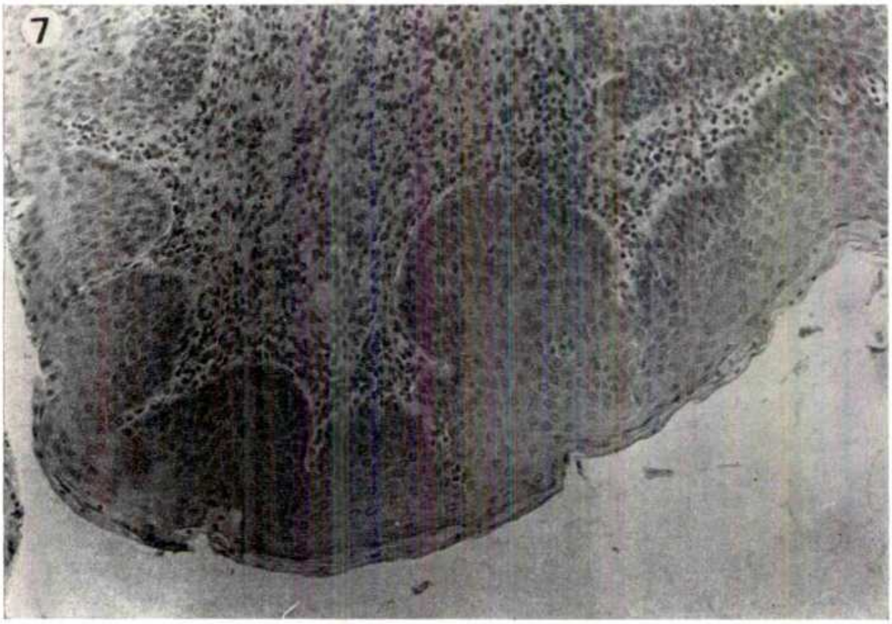

Fig. 6. High urothelium with vesiculated and ballooned cells from the bladder mucosa at the level of the free end of the prosthesis. H & E. × 70.

Fig. 7. Squamous epithelium from the bladder mucosa close to the entrance of the prosthesis. H & E. × 70.

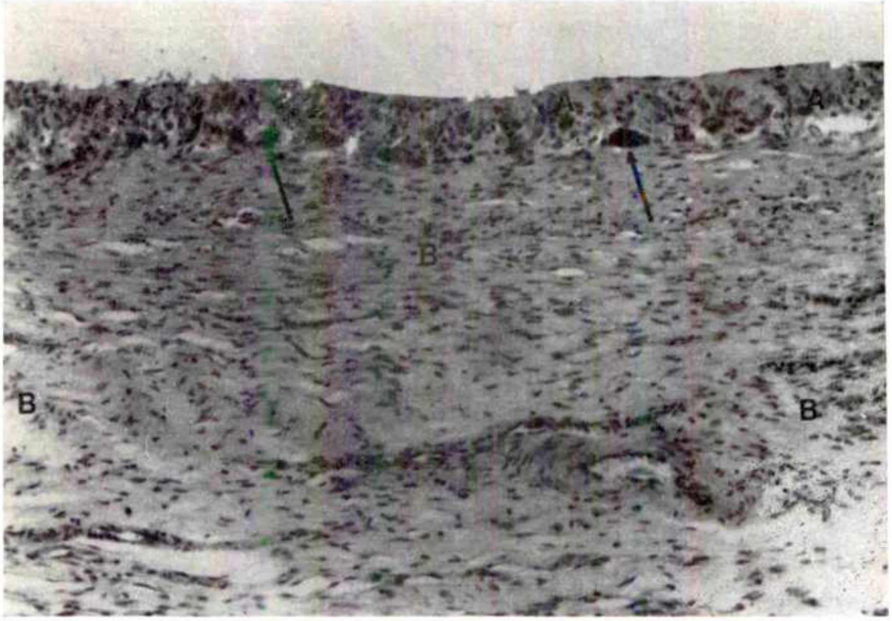

Fig. 8. Fibrous membrane surrounding prosthesis. Zone of macrophages simulating epithelial lining (A). Fibrous membrane (B). Foreign body giant cells (↑). H & E. ×70.

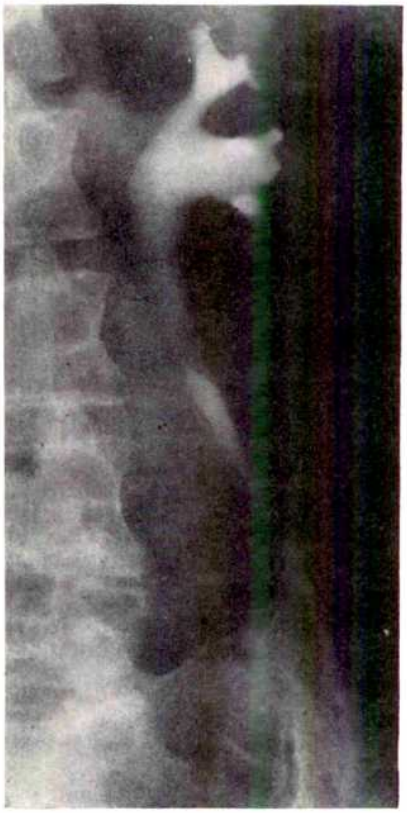

Fig. 9. Cystogram of a 68-year-old woman (case 1) 15 months after insertion of an ureter prosthesis showing low pressure reflux and a normal pyelogram.

months showed steady improvement: the right kidney became normal, the function of the left kidney was still impaired but the prosthesis was functioning well. A cystogram showed low pressure reflux into the prosthesis which appeared "well healed" into the bladder on cystoscopy. (Fig. 9).

Case 2. A 39-year-old woman treated by radiotherapy for carcinoma of the cervix in 1970, re-admitted in June 1972 in anuria with severe uraemia. Retrograde pyelograms showed complete block of both ureters at the level of L II. Right-sided nephrostomy was performed, but there was no resultant diuresis. Peritoneal dialysis was instituted, and the patient's condition improved. Laparotomy was undertaken 1 week later, and both ureters were obliterated by carcinomatous invasion, but the liver and peritoneum were not involved. Both ureters were excised, and prostheses were placed on both sides. Function of the left kidney was restored within 1 week. One month later the left prosthesis was replaced by one of smaller diameter because of leakage at the pelvic anastomosis. Four months later an abscess formed at the pelvic anastomosis of the right prosthesis. The abscess was drained, and subsequently, prosthesis and the kidney, which had never functioned, were removed. Cystoscopy showed good "healing in" of the left prosthesis with mild squamous metaplasia. Repeated intravenous urograms showed normal function of the left kidney throughout the period after insertion of the prosthesis. The patient died with carcinomatosis 6 months after the left prosthesis had been replaced. At postmortem, the left kidney and pelvis were of normal size, but invested with tumour tissue. The prosthesis was patent.

Discussion

The prosthesis used in the present study has previously been tested in 11 dogs with 16 prostheses in all (Blondell, 1972). Three dogs died postoperatively: 1 from urinary leakage, 1 from stenosis at the upper anastomosis complicated by pyonephrosis and finally 1 following urography. In 8 cases with an average observation period of 6 months the results were good. Our results have confirmed that Scurasil^{R} produces little tissue reaction, but in all cases a fibrous membrane containing macrophages is found surrounding the prosthesis, an indication of tissue reaction to a foreign body.

In experiments with dogs Sausse and associates (1973) found a newly developed urothelium surrounding the prosthesis. In the present investigation no basement membrane could be demonstrated and the cells around the prosthesis appeared morphologically as macrophages, some of them containing several nuclei.

As in Blondell's study calcifications around the prosthesis and bone formation around the anastomoses were found. At the level of the free end of the prosthesis in the bladder and—less pronounced—in the pelvis hypertrophy of the urothelium was demonstrated with a squamous epithelial metaplasia near the entrance of the prosthesis. This change may be caused by simple mechanical irritation. The inside of the prosthesis was covered by a proteinaceous material, but no incrustation was demonstrated.

The fixation of the prosthesis to pelvis and bladder was not satisfactory as migration occurred at the pelvic anastomosis in 1 case and at the vesical anastomosis in 2 cases. The migration, however, occurred at a late time when a fibrous membrane had been formed around the prosthesis and no urinary leakage was present.

Blondell found that the anti-reflux valve was not completely sufficient. Minor low pressure reflux but no high pressure reflux occurred meaning that the kidney would not be exposed to high pressures. This particular problem has not been examined in the present study, but in a preliminary investigation similar observations were made. The valve prevented reflux when the pressure exceeded 20 cm of water.

One of the purposes of this study was to examine if a ureteral prosthesis with no propulsion of urine would cause hydronephrosis and a decrease in kidney function. The urograms were normal 1 month after ureteral replacement and postmortem examinations 6-8 months after operation showed no hydronephrosis. The kidney function was normal in all cases.

The increase of the concentrations of creatinine and urea in plasma seen during the first days after surgery (Figs. 3 and 4) are, except for pig no. 3, similar to that found in unilaterally nephrectomised pigs (Gyrd-Hansen *et al.*, 1969). The far greater rise of the concentration of creatinine and urea in the plasma of pig no. 3 indicates severe renal failure in the first 2 or 3 days after operation. After about a week the creatinine and urea values were stabilised in all 5 pigs and similar to those found in unilaterally nephrectomised pigs.

The inulin, endogenous creatinine, urea and PAH clearances measured 1 month after surgery are a little higher than the corresponding average values found by Gyrd Hansen (1968) in unilaterally nephrectomised pigs, but the difference is not statistically significant. 6 to 8 months after operation the renal clearances and plasma and blood flow had decreased somewhat, but were still on an average higher—both per 10 kg body weight, and per 100 g kidney tissue—than in unilaterally nephrectomised pigs 3 to 4 months after nephrectomy. The differences were again not significant.

The present study has confirmed that the Scurasil^R prosthesis (the latest model) produces little tissue reaction; it gives no incrustations or other obstructions and dislodgement is late and without clinical significance. Furthermore it has been demonstrated that no hydronephrosis develops and that the kidney function remains normal, even after 8 months.

The encouraging results of the experimental studies led to a clinical trial of the prosthesis in 2 women with ureteric obstruction, a late complication of radiotherapy for carcinoma of the cervix. It is evident from Auvert *et al.* (1970), Wagenknecht (1971) and our experience that this prosthesis can ensure urinary drainage with no urinary diversion in patients with short life expectancy. It may be that indications for use of the prosthesis are wider, but this can only be determined by carefully conducted trials and long follow-up periods.

Summary

Five pigs of the Danish Landrace breed had one ureter totally replaced with a Scurasil^R prosthesis provided with Rhodergon^R cuffs and an anti-reflux valve. The opposite kidney was removed simultaneously.

There were no postoperative complications. All pigs survived an observation period of 6 to 8 months. There were no signs of hydronephrosis or urine leakage and the kidney function remained normal. Postmortem examinations showed foreign body reaction adjacent to the prosthesis but this was without clinical significance.

As a consequence of these results, the prosthesis was used in 2 women with ureteric obstruction after radiotherapy for carcinoma of the cervix. The results may be described as satisfactory.

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Intraperitoneal Rupture of the Bladder

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Intraperitoneal rupture of the bladder is much less common than extraperitoneal rupture in the proportion of about 1:6 (Requarth, 1959).

11 cases of intraperitoneal rupture of the bladder due to closed abdominal injury without injury to the bony pelvis seen at Mulago Hospital, Kampala in the 3 years 1969-71 demonstrated some instructive features of this type of injury.

Patients

All the 11 patients were men, 10 of them being between 18 and 32 years of age; the other patient was 48 years old.

Mechanism of Injury

At least 5 of them had been drinking heavily prior to injury. The cause of the rupture in 7 cases was a blow in the abdomen, usually a kick (see Table I). The other 4 patients were pedestrians struck by passing vehicles, and 3 of those also had fracture of the tibia. With this exception associated injuries were not common (see Table I and Table II).

Table I

	Age	Sex	Cause	Recent Alcohol	Ass. Inj.	Delay in Treatment (hours)	BP mm Hg Systolic	Pulse Rate/ min	Post Op. Blood	IP/ Days	Post Op. Com- plication
1.	23	M	Blow	...	...	96	120	80	No	6	...
2.	31	M	Pedestrian R.T.A.	...	# tibia	48	110	80	Yes	11	...
3.	21	M	Assault	Yes	...	48	130	80	No	8	...
4.	23	M	Assault	...	...	30	120	110	Yes	8	...
5.	27	M	Assault	Yes	...	48	120	80	Yes	9	...
6.	18	M	Pedestrian R.T.A.	Yes	# tibia post. ureth. tear	22	110	120	Yes	11	Urethral stricture
7.	26	M	Assault	...	...	20	130	90	Yes	12	...
8.	32	M	Assault	Yes	...	16	120	82	No	8	...
9.	27	M	Assault	...	...	9	110	82	Yes	8	...
10.	48	M	Pedestrian R.T.A.	Yes	...	12	130	84	Yes	15	...
11.	19	M	Pedestrian R.T.A.	...	# tibia Colles # ileal tear	18	130	96	No	8	Urinary infection Wound infection

One of the features of this series was the delay experienced by the patients in obtaining definitive treatment (see Table I). In 5 of the 11 patients there were delays of from 1 to 4 days before operation was undertaken. In the other 6 patients the delay was less than 24 hours, the shortest time being 9 hours.

Table II

Associated Injuries

Fractured tibia	3
Colles fracture	1
Ileal tear	1
Partial tear urethra	1
Fractured pelvis	Nil

Symptoms

At the time of original trauma all the patients experienced lower abdominal pain. The symptoms at the time of admission are tabulated in Table III. The main finding was abdominal pain as a constant symptom. This was generalised in 9 patients, and localised to the suprapubic region in 2. The pain was judged to be severe in 4 cases.

Table III

Symptoms on Admission

Abdominal pain—generalized	9	11
Abdominal pain—in hypogastrium	2	
Abdominal pain severe	4	
Failure to pass urine	11	
Vomiting	4	
Hiccoughs	1	
Bowels opened since trauma	1	

None of the patients had passed urine spontaneously between the time of rupture and admission to hospital. Four of the patients had been vomiting, and 1 patient was hiccoughing on admission. Rather surprisingly 1 patient had a normal bowel action after sustaining his bladder rupture.

Table IV

Abdominal Signs on Admission

Abdominal tenderness	11
Impalpable bladder	11
Free fluid and shifting dullness	2
Abdominal distension	4
Normal bowel sounds	2
Febrile	0

Signs (See Table IV)

Despite the delay in treatment the condition of these patients was surprisingly good. Few were considered to be suffering from shock on admission to hospital, and as can be seen from Table I, the systolic blood pressure on admission was in the range 110 to 130 mm Hg. The pulse rate was usually slightly raised, being in the range of 80 to 96/min. However, in 2 cases, see Table I, the rate was 110/min and 120/min respectively.

All of the patients had tenderness in the abdomen, and none had a palpable bladder on admission. In 4 patients abdominal distension was present. In only 2 of the patients were signs of free intra-abdominal fluid elicited. This is somewhat unexpected as in all cases, there was, at operation, a considerable quantity of free urine present in the abdomen, in 1 case as much as 4 litres. Surprisingly in 2 of the patients normal bowel sounds were heard. None of the patients was febrile on admission.

Investigations

Six of the patients were catheterised, 2 of them in the operating theatre. In 2 of these patients a little blood-stained urine was obtained. In 3 other of these 6 patients no urine at all was obtained on passing a urethral catheter which made the diagnosis virtually certain in these patients. The 6th patient (No. 1 in Table I) is interesting. After the injury he complained of inability to pass urine. He was thought to have retention of urine and was catheterised. About 1 litre of urine was withdrawn. He subsequently failed to pass urine spontaneously for the next 3 days. On each of these days he was catheterised with withdrawal of normal urine in fact from the peritoneal cavity via the tear in the bladder. He was then referred for definitive treatment.

In 2 of the 11 patients the abdomens were aspirated with a fine needle and syringe. In both these patients blood-stained urine was aspirated.

Treatment

Because of the relatively good clinical state of the patients none of them had any significant blood transfusion before operation. When bladder rupture was considered as a likely diagnosis laparotomy was carried out. The tear in the superior surface or dome of the bladder was usually obvious, and varied in length from an estimated 2·5 cm to 10 cm. There was usually about 2 litres of blood-stained urine in the abdomen. Peritoneal inflammation was minimal.

The tear in the bladder was closed with 2 layers of continuous catgut, the inner layer being non-chromic and the outer layer chromic.

The bladder was drained in each case by a Foley catheter per urethram, retropubic tissue drainage being provided in 5 patients. One of the patients (No. 7 in Table I) had a suprapubic catheter in addition to the urethral catheter.

Postoperative care

Seven of the 11 patients had a blood transfusion, usually 2 units postoperatively. All were given antibiotics postoperatively: 7 of the 11 received combined treatment with penicillin and streptomycin. Three received tetracycline and 1 patient chloramphenicol. The Foley catheter was left in about 8 days on average and the patient had no difficulty in voiding subsequently. The average stay in hospital was 10 days.

Complications (See Table V)

There were no deaths. One patient had a postoperative urinary infection which resolved rapidly when the antibiotic was changed. The patient who had an intraperitoneal bladder rupture as well as a partial tear of the posterior urethra was found at follow-up 2 months later to have developed a posterior urethral stricture; this required bouginage.

Table V

Complications

Wound infection	1
Urinary infection	1
Urethral stricture	1

Comment

Intraperitoneal rupture of the bladder, in the absence of pelvic fracture is usually caused by a blow on the lower abdomen. In the present series it occurred typically among young men who had recently been drinking.

One particular feature of this group of patients was the delay in receiving definitive treatment, partly because most patients lived some distance from the hospital. Also, the presence of more obvious injuries, such as fractured tibia, may have initially diverted the medical attendant's attention from the abdomen. The postmortem records of the hospital for this 3-year period were examined. Only 1 death is recorded as due to undiagnosed rupture of the bladder as the sole cause of death—and this was undiagnosed during life. It would seem, therefore, that the prognosis of those patients who reach hospital with this condition is good provided it is recognised.

The history of a lower abdominal blow, subsequent abdominal pain and tenderness and an inability to pass urine is very suggestive of intra-peritoneal rupture of the bladder and should alert the medical personnel to such a possibility. *Aspiration of the abdomen* was positive on both occasions when it was used. Although negative aspiration does not exclude the diagnosis, a positive aspiration gives rapid confirmation of a ruptured bladder. The technique is easy to perform, safe and could have been used more frequently.

Rieser and Nicholas (1963) have advocated retrograde cystograms in the diagnosis of this condition, but these were not used here, mainly for technical reasons.

As stated earlier, a urethral catheter was passed on 6 patients. This procedure was helpful on 5 occasions. On the other occasion the catheter passed through the rent in the bladder to the peritoneal cavity and drained the urine which delayed the diagnosis for several days.

At operation the relative absence of peritoneal inflammation was one of the more noticeable features. The peritoneum was remarkably "clean" when compared with that of, say, a long-standing perforated duodenal ulcer. It was said by Bacon (1943) that "bacterial peritonitis promptly occurs in 60% of such cases" with consequent high mortality. This was not the experience here. The patients in this series were not in shock. This is in line with experience elsewhere. Rieser and Nicholas (1963) found only 3% of their cases of ruptured bladder had shock attributable to the bladder injury. It would seem that infection of the urine in the peritoneal cavity is of critical importance. If the urine remains uninfected the patients are relatively well, have minimal peritonitis and have a good prognosis; but should the urine become infected the patients develop shock with a severe peritonitis and have a poor prognosis.

It has been found by Wing *et al.* (1971) that the urinary pH of Africans in Kampala is higher than that of Asians and Europeans. This is attributed to dietary factors. At higher pH the growth of *E. coli* is inhibited, and this may account for the relative freedom from infection of the peritoneal cavity seen in these patients at operation. Kwang Wook Ko *et al.* (1964) successfully treated a girl 3½ years old with an 8-day-old intraperitoneal rupture of the bladder. They suggested that she survived for so long before definitive treatment because she was equilibrating the bladder urine with her extra-cellular fluids through the peritoneal surface. The reabsorption of urinary constituents led eventually to uraemia and hyperkalaemia. This feedback self-dialysis system presumably would stop functioning once infection supervened.

Rieser and Nicholas (1963) strongly advocate the use of a suprapubic cystostomy in addition to a urethral catheter. This additional catheter was used in only 1 patient. None of the patients suffered from a dehiscence of the bladder repair; a urethral catheter alone would seem to be adequate.

Two points emerge from this small series.

The prognosis would seem to be good as long as the intra-abdominal urine is not infected.

A well-draining urethral catheter is adequate in the postoperative management of these patients.

Summary

11 cases of intraperitoneal rupture of the bladder were seen in a 3-year period at Mulago Hospital, Uganda.

The presentation and management are described and possible reasons for the good prognosis are discussed.

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Methotrexate Treatment for Advanced Bladder Cancer

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Patients with advanced carcinoma of the bladder that recurs or persists after conventional forms of therapy have a poor prognosis, and when distant metastases develop, survival is seldom for longer than a few months. In recent years, cytotoxic drugs have provided a possible form of treatment for patients with such extensive disease.

In the management of carcinoma of the bladder, a great number of cytotoxic agents have been tried in a relatively small number of patients (Pavone-Macaluso, 1971). That used most commonly, alone or in combination with radiotherapy, has been 5-fluorouracil (Woodruff, Murphy and Hodson, 1963; Stein and Kaufman, 1968; Edland, Wear and Ansfield, 1970). The report by Prout *et al.* (1968) concerning the importance of a placebo in a clinical trial of this drug casts doubt on its effectiveness, and indeed emphasises the necessity for more critical evaluation when investigating the role of any cytotoxic agent for bladder cancer.

Table I

Published Reports on Methotrexate Therapy for Bladder Carcinoma

Author	Method of Administration	Cases Treated	Cases Responding	Nature of Response
Altman *et al.* (1972)	Intermittent i.v	11	4	"Complete regression of visible tumour"—1 case; "Mass became smaller and softer"—3 cases
Andrews and Wilson (1967)	Intermittent i.v	1	0	No details
Burn (1966)	Continuous i.a	6	2	"Partial regression of tumour mass"
Pavone-Macaluso (1971)	Not stated	5	0	No details
Sullivan (1962)	Continuous i.a	3	3	"Sustained clinical benefit and decrease in tumour size"
Talley (1970)	Not stated	1	1	"Transient response"
Tindel (1967)	Continuous i.a	1	0	Not stated
	Total	28	10 (36%)	

i.v. = intravenous.
i.a. = intra-arterial.

Methotrexate has been used infrequently for the treatment of transitional cell carcinoma of the bladder. It was decided to try this drug in our clinic because early reports had suggested that it was capable of producing regression of solid tumours (Condit *et al.*, 1964; Papac, Lefkowitz and

Bertino, 1967), including bladder cancer (Foley *et al.*, 1967), when given orally or by intravenous injection. Sullivan (1962) and Burn (1966) had also observed responses in advanced bladder tumours following treatment with this drug by continuous intra-arterial infusion. Abbassian and Wallace (1966) used methotrexate by intra-vesical instillation in three patients with diffuse non-infiltrating tumours of the bladder without success. Collected results from the literature show tumour regression in 36% of 28 cases of bladder cancer treated with systemic methotrexate (Table I). Such a degree of success is encouraging, but the evidence of tumour response in some of these cases has been poorly documented and the duration of remission seldom stated.

The present report concerns the use of comparatively high dose, intermittent, intravenous methotrexate for advanced transitional cell carcinoma of the urothelium.

Patients and Protocol

40 patients with advanced carcinoma of the bladder with or without distant metastases, and 2 with tumours arising in the renal pelvis have been treated with methotrexate in the Urology Unit of the Royal Marsden Hospital. In every case the primary disease has been proven by biopsy or operative specimen to be a transitional cell carcinoma, and when metastases were present there was no evidence of a new primary tumour.

The case material has been divided into 3 groups according to the nature and extent of the disease:

Group I (6 cases). Primary treatment for previously untreated advanced tumours of the bladder or renal pelvis in patients generally unsuitable for palliative surgery or radiotherapy.

Group II (19 cases). Treatment for tumours of the bladder persisting or recurring after radiotherapy, which had been palliative in 12 cases and radical in 7.

Group III (17 cases). Initial treatment for metastases with or without tumour in the bladder. 15 patients had distant metastases and 2 others had deposits in pelvic and para-aortic lymph nodes. The primary tumour had been treated with preoperative irradiation and cystectomy (3 cases), radio-gold seed implantation (1 case), radical external beam irradiation (2 cases) and palliative irradiation (6 cases). Four other patients presented with metastases having received no prior treatment, whilst a fifth had received local irradiation for metastatic lymph nodes.

Before commencing treatment the full extent of the disease was carefully assessed and the measurable parameters recorded. Full blood count, blood urea, creatinine clearance and intravenous pyelogram were carried out. The plan was to give methotrexate in doses of 50 to 100 mg intravenously every 1 to 2 weeks on an out-patient basis. If renal function was moderately impaired at the outset (creatinine clearance 50 to 80 ml per minute), a preliminary test dose of 25 mg was given and if this was well tolerated, 50 to 75 mg was given in subsequent injections. To assist urinary excretion and thereby reduce toxicity, oral frusemide, 40 mg, was often prescribed the following day.

At each out-patient visit a full blood count and blood urea were estimated. If the total white cell count fell below 3,000 per mm^3, the platelet count below 100,000 per mm^3, or the patient developed oral ulceration, vomiting or diarrhoea, treatment was deferred until recovery. Treatment was then recommenced at a reduced dose and/or a greater time interval between doses. With lesser toxicity such as nausea, malaise, or skin reactions, the dose was reduced but regular treatment maintained. If there was deterioration of renal function (usually as a result of progressive urinary obstruction by tumour) the dose was always reduced because the risks from leukopenia, thrombocytopenia and intestinal ulceration were known to be considerable.

The patients' progress was followed by means of clinical examination, cystoscopy and bimanual assessment under general anaesthesia with biopsy if necessary, and serial radiological examinations when appropriate. Treatment was maintained unless there was objective evidence of tumour progression and clinical deterioration, or the severity of side-effects made the quality of survival unacceptable.

In assessing the results of treatment *complete regression* has been defined as the complete disappearance of all detectable carcinoma. *Partial regression* implied undoubted decrease in size of clinically or radiologically measurable disease, or the arrest of growth in a previously rapidly advancing tumour. Many patients reported relief of symptoms such as haematuria, frequency, pain or breathlessness, but subjective criteria alone have been ignored in evaluating treatment.

Results

11 of the 42 patients (26%) treated with methotrexate showed objective evidence of tumour regression: in 3 this was complete (Table II). In no case was regression permanent. The extent of disease in each case, together with the nature and duration of response, is summarised in Table III. In the first 8 cases the response was considered worthwhile in terms of the quality and probable extension of survival. Although there was some evidence of a tumour response in the 3 remaining cases the patients themselves experienced no practical benefit.

Table II

Incidence of Tumour Regression According to Site in Royal Marsden Hospital Series

Group	Tumour and Treatment	Number of Patients	Tumour Regression Complete	 Partial	 Nil	Total Cases Responding
I	Initial treatment for advanced tumour in bladder (4 cases) or renal pelvis (2 cases)	6	0	2	4	2
II	Treatment for persistent or recurrent tumour in bladder after radiotherapy	19	1	2	16	3
III	Initial treatment for metastases	17	2	4	11	6
	Total	42	3	8	31	11 (26%)

In 31 patients there was no evidence of tumour regression that could be attributed to methotrexate. Some of these gained symptomatic relief and in others the disease was stationary or grew only very slowly over several months. In retrospect, it is likely that the improvement in these cases was due to the control of infection or to fluctuation in the natural history of the disease, but some benefit from methotrexate cannot be ruled out. Treatment was stopped in 22 patients because it was considered to be ineffective: in 5, toxicity prevented further administration of the drug, and 4 died of their disease during therapy. No deaths were attributable to methotrexate treatment itself.

Dose

Treatment results have been correlated with dosage, based on milligrammes of methotrexate given per month (Dahl, Gregory and Sheuer, 1972) as well as the total amount during the entire treatment. No relation was found between the amount of drug given and the result observed. There was considerable variation in the amount of drug administered: the mean monthly dose in those responding to treatment was 170 mg (range 79 to 317 mg) and for the failures, 125 mg per month (range 38 to 329 mg). This difference is not statistically significant.

Toxicity

In 29 of the 42 patients the side-effects due to methotrexate were sufficiently severe to interrupt treatment for 2 weeks or more. The nature and incidence of toxicity are shown in Tables IV and V.

There was no correlation between toxicity and tumour regression (7 of 11 patients showing a response developed side-effects, as did 22 of 31 failures), nor between toxicity and dosage in the range used. In the majority of cases, recovery from toxic effects was rapid and it was possible to continue treatment after a short interval.

Table III

Clinical Data of 11 Patients showing Tumour Regression Following Methotrexate Therapy in Royal Marsden Hospital Series

Group	Case Sex, Age	Tumour Extent	Nature of Regression	Outcome
I	J.H. M, 65	T4*, infiltrating abdominal wall	Arrest of tumour growth for 15 months	Treatment stopped: tumour relapsed
	E.C. M, 70	Multiple T1	"Very small tumours" at postmortem	Died myocardial infarct after 4 months treatment
II	E.C. M, 79	Persistent T4 and new multiple T1	Tumour free after 8 months	Treatment stopped: symptoms returned 5 months later; died myocardial infarct
	S.J. M, 79	Recurrent T3	Small slough at tumour site after 6 months	Treatment stopped: developed metastases
	G.S. M, 63	Persistent T4	Arrest of tumour growth for 20 months	Alive and well
III	R.S. M, 78	Pulmonary and mediastinal metastases	50% regression for 6 months	Relapsed despite continued therapy
	F.H. M, 71	Pulmonary metastases and untreated T4	50% regression of metastases for 12 months; no effect on primary tumour	Relapsed despite continued therapy
	H.E. M, 69	Persistent T4 and bone metastases	Partial regression of metastases for 6 months	Relapsed despite continued treatment
	D.G. F, 56	Multiple cutaneous deposits and palpable pelvic nodes	Complete regression within 6 weeks	Treatment stopped: metastases developed
	F.C. M, 62	Metastatic cervical nodes	Complete regression within 4 weeks following single injection	Nodes returned after 2 months; no response to repeated treatment
	T.H. M, 66	Metastatic pelvic nodes (palpable)	Complete regression after 8 weeks	Relapsed after 7 months despite continued treatment

* = T Stage, Classification of International Union Against Cancer.

Table IV

Incidence of Toxicity Following Intravenous Methotrexate Administration in 42 Patients

Side-effects	No. of Patients*
Oral Ulceration	19
W.B.C. $< 3{,}000/\text{mm}^3$ ± Platelets $< 100{,}000/\text{mm}^3$	15
Vomiting/Nausea	10
Diarrhoea	8
Malaise	10
Skin reactions	3

* Some patients had more than one side-effect.

Previous Radiotherapy

Of 21 cases in groups II and III who had persistent or recurrent tumour in the bladder after radiotherapy, 3 showed regression with methotrexate. Two out of 4 previously unirradiated tumours responded to this agent. The interval between radiotherapy and commencing methotrexate in the 3 successful cases was 3, 5 and 30 months following a dose of 4,000 to 4,700 rads for stage T4, T3 and T4 tumours, respectively (U.I.C.C. classification).

Table V

Incidence of Multiple Side-effects of Methotrexate in 42 Patients

No. of Toxic Manifestations per Patient	No. of Patients
None	13
One	13
Two	6
Three	2
Four	6
Five	2

29/42 had clinically significant toxicity

Discussion

Two conclusions may be drawn from this study. First, methotrexate is capable of arresting tumour growth in a small but significant proportion of patients with advanced bladder cancer for whom local treatment is no longer feasible. Second, appreciable side-effects occur frequently when this drug is given in doses of 25 to 100 mg by single intravenous injections at 1- or 2-week intervals.

Prout *et al.* (1968) made a valuable contribution by reporting the unexpected results of a double-blind trial in which 5-fluorouracil was compared with a placebo for bladder cancer. In some cases they observed that tumour size, assessed clinically, actually appeared to decrease during the administration of the placebo when measured over a 60-day period. It was also interesting that moderate haemopoietic depression, nausea, diarrhoea and malaise sometimes accompanied placebo administration, and were considered by Prout *et al.* (1968) to be due to the tumour rather than to the "treatment". In view of these observations we have been particularly critical in evaluating our results and have rejected any case of doubtful tumour regression or of apparent drug toxicity that could have been due to the disease rather than to treatment.

Spontaneous regression of transitional cell carcinoma of the bladder is very rare (Everson and Cole, 1966). Our criteria for accepting tumour arrest as being due to treatment have been strict and we believe that the changes observed in the 11 cases reported here are attributable to methotrexate therapy. Furthermore, from our experience with this agent given for periods up to 2 years, the side-effects (oral ulceration, vomiting, depression of white blood cell count below 2,000 cell per mm^3 and platelets below 100,000 per mm^3), occurring with treatment and improving or absent when treatment was withheld, were undoubtedly due to the drug and not to products of the tumour itself.

Toxicity was a major disadvantage of the regime used in this study. In the majority of patients it was not very serious, but in 1 man it was almost fatal. Many of the patients had impaired renal function and this undoubtedly played a major role in the high incidence of side-effects. Miller *et al.* (1961) demonstrated that the toxic effects of methotrexate depended more upon time factors than on dose *per se*. Recent infusion studies at this hospital (Goldie, Price and Harrap, 1972) indicate that the toxicity of this drug is largely avoidable if the duration of each administration does not exceed 30 hours and is followed immediately by folinic acid "rescue". Careful monitoring of renal function is essential in all patients before and during methotrexate therapy. In this respect it is important to realise that in a patient with reduced renal clearance a single injection of methotrexate may produce plasma levels of the drug comparable to a 24-hour infusion (Price, 1973). Administration of methotrexate itself may lead to renal tubular damage and impaired renal function (Condit, Chanes and Joel, 1969).

Adequate renal function was mandatory for inclusion in the chemotherapy trials for bladder cancer reported by Altman *et al.* (1972) and by Prout *et al.* (1968). Such a requirement would exclude many of the patients with advanced bladder tumours for whom chemotherapy is the only remaining treatment possible.

The failure of methotrexate to be more effective may have been due to 2 factors:

(*a*) Inherent or rapidly acquired resistance of the tumour to this agent which is known to occur *in vitro* (Jacobson, 1966). So far, little can be done to overcome such resistance in clinical practice.

(*b*) Inadequate treatment of tumours that were potentially responsive. Toxicity prevented regular treatment in many patients and often necessitated reduction of the methotrexate dosage to less than 100 mg per month which is probably sub-optimal (Price, 1973). It is interesting that only 4 of 11 patients showing an initial response relapsed while continuing treatment. In 5 of the remaining 7 cases treatment was stopped because remission appeared to be stable, but all 5 relapsed within a few weeks. In 2 patients, 1 with pulmonary metastases and the other with a large pelvic tumour invading the abdominal wall, considerable tumour regression occurred, only to relapse whilst the patients were abroad on holiday for 1 month without treatment: further regression was promptly achieved with resumption of injections. These observations suggest that inadequate treatment may well have been a contributory factor in the cases that failed in this study: more intensive therapy might have achieved more frequent and more complete tumour control.

Johnston (1966) suggested that previous radiotherapy may reduce the effectiveness of methotrexate. Many of the patients in the present study had received radiotherapy in the past but a relationship between irradiation and subsequent response to chemotherapy could not be determined from our small series. With Irvine (1966) we think that external radiation was not harmful in this respect but that tumours in these circumstances have reached a more advanced stage, both biologically and anatomically, and have become more resistant to all forms of treatment.

Conclusions

A significant number of patients with advanced transitional cell carcinoma of the bladder derived benefit from treatment with intermittent intravenous methotrexate. Results may be improved and toxicity reduced by modifying the method of administration. The following criteria may assist in achieving this aim:

1. Regular intermittent intravenous methotrexate in higher doses given by 6- to 12-hour infusion when renal function is normal, or by single intravenous injection when this is impaired.
2. Addition of folinic acid "rescue" 18 to 24 hours after commencing the infusion or giving the injection.
3. Continuation of regular intermittent cytotoxic therapy for long periods, or indefinitely, even when tumour regression appears to be complete.

Summary

Intermittent intravenous methotrexate has been used to treat patients with locally advanced or metastatic transitional cell carcinoma of the bladder (40 cases) and of the renal pelvis (2 cases).

Objective evidence of tumour regression, attributable to the methotrexate therapy, was observed in 11 patients (26%) for 2 to 20 months. Several other patients gained relief of symptoms but in these there was no clear evidence of tumour regression.

Toxic side-effects from methotrexate interrupted treatment for a time in 29 patients but were seldom serious and were never fatal.

It is concluded that intravenous methotrexate therapy is of value in the management of advanced bladder cancer.

The possibility of improving tumour response and decreasing drug toxicity is discussed.

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Urinary Manometry in Spinal Cord Injury: a Follow-up Study. Value of Cysto-Sphincterometrography as an Indication for Sphincterotomy

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Two factors may intervene in the failure of the neurogenic bladder to empty: lack of co-ordination and contraction of the detrusor, and increased urethral resistance. Increase in urethral resistance may be due to inadequate opening of the bladder neck, the external sphincter, or both.

Dysfunction of the external sphincter may be due to one of the following: spasticity of the sphincter, part of a general spasticity of the muscles of the pelvic floor; hyperreflexia of the sphincter (Bors, 1964), which responds spasmodically to exteroceptive stimuli from the bladder, urethral, and anal mucosa (Rossier and Bors, 1964); bladder-sphincter inco-ordination (loss of reflex inhibition of the sphincter at the moment of detrusor contraction); reflex contraction of the sphincter in response to increased intra-abdominal pressure (Newman, 1949), or the Credé manoeuvre (Rossier, 1964); or fibrotic stenosis of the sphincter, in cases of long standing spinal cord injury (Cukier *et al.*, 1971). Pudendal nerve section, which denervates the pelvic floor muscles, except the levator ani[1], has given satisfactory results, but has certain disadvantages: the operation is technically difficult, and because of the frequent anatomical variations, is occasionally incomplete. Both bilateral and unilateral pudendal neurectomy may result in loss of erection. Section of the pudendal nerve naturally has no effect on a sclerosed sphincter.

Since Cosbie Ross, Damanski and Gibbon (1957) proposed transurethral sphincterotomy, many others have published results of this procedure: therapeutic success seems to be of the order of 50% to 60% (Currie *et al.*, 1970; Cosbie Ross, Gibbon and Damanski, 1963; Tsuji *et al.*, 1965) and up to 87% in the small series reported by Smythe (1966). Malament (1972), O'Flynn (1972), Retief (1970), Cosbie Ross (1968) and Tsuji *et al.* (1967), have reported 87% to 100% "satisfactory" results, without, however, defining their criteria of success. We felt, therefore, that a more precise analysis was in order, of the results obtained in 28 of our patients.

Patients and Methods

(a) Patients

One of us (R. O.) performed transurethral sphincterotomy in 28 male patients: 13 were tetraplegic (6 complete lesions, 7 incomplete); 15 were paraplegic (all complete lesions, 1 of lower motor neurone type). 24 patients were spastic; 4 were flaccid although 3 of these with epiconal lesions, had conus reflexes and upper motor neurone type of bladder dysfunction, 1 patient had visceral and somatic lower motor neurone lesion dysfunction. 17 patients were operated upon within

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[1] Our own clinical experience leads us to support the classical concept that the innervation of the external urethral sphincter is via the internal pudendal nerve, contrary to the theory of Gil Vernet (1964) based on his numerous histopathological studies.

1 year (average 5 months) of their injury; the other patients had been paralysed from 2 to 16 years before operation.

(b) Technique

The diagnosis of spasticity of the external urethral sphincter was made on the basis of cysto-sphincterometrography in 17 of the cases before operation. This investigation was carried out on each of the 28 cases after operation.

The initial method described by Rossier and Bors (1970) underwent several subsequent changes; it consisted of measuring the pressures within the bladder, the urethra, the rectum and the external anal sphincter (Fig. 1, A).

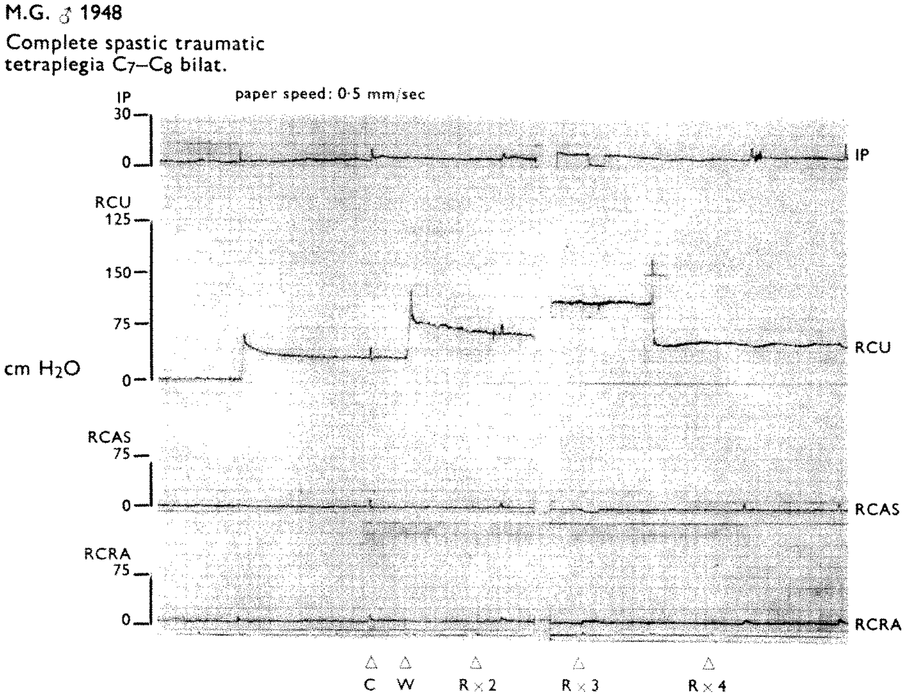

Fig. 1. A, Cysto-sphincterometrography, before sphincterotomy: IP—Intravesical pressure. RCU—Intra-urethral resistance. RCAS—External anal sphincter pressure. RCRA—Intrarectal pressure. C—Credé manoeuvre. W—Withdrawal of intra-urethral Reynolds balloon catheter. RX2—Balloon of intra-urethral Reynolds catheter positioned in the membranous urethra (U2) (see corresponding X-ray, Fig. 1, B) RX3—Balloon of intra-urethral Reynolds catheter positioned distally in the external urethral sphincter (U3) (see Fig. 1, C). RX4—Balloon of intra-urethral Reynolds catheter positioned at the first bend of urethra (U4) (see Fig. 1, D).

Intravesical pressures were recorded via a French No. 7 ureteral catheter; intra-urethral, intrarectal and intra-anal pressures were recorded via Reynolds[1] balloon catheters (7 Fr. UB31), with radio-opaque markings at each end of the balloon allowing constant surveillance of their location with image intensifier and video-tape monitoring. Topographic relationships were more precisely determined on the oblique films made, with the aid of a 5 mm grid incorporated in the X-ray cassette (see Fig. 1, B). The intravesical, intrarectal and intra-anal catheters remained in place for the duration of recordings, while the balloon of the intra-urethral catheter was progressively withdrawn from the bladder, through the bladder neck, the urethra just below the bladder neck (U1), the portion of the urethra surrounded by the external urethral sphincter, the membranous urethra (U2), the portion of the urethra surrounded by the distal part of the external urethral sphincter (just before the beginning of the bulbous urethra, U3), and through the spongy urethra at its first bend (U4) (Fig. 1 B, C and D). All the pressure recordings made within the membranous urethra (U2 and U3) were carried out while the bladder was in a resting state.

In males, U3 was more precisely defined as the portion of the membranous urethra surrounded by the urogenital diaphragm, containing the distal portion of the urethral sphincter and part of the deep transverse perineal muscle, in close proximity to the bulbospongiosus muscle, including the muscle *compressor nudae* (Morales and Romanus,

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[1] P. J. Reynolds Ltd, Medical Electronics, London N21, England.

1953). On slightly oblique X-ray of the pelvis, the balloon placed at U3 is seen to straddle the inferior pubic ramus (see Fig. 1, c).

. In each case where micturition was possible, voiding cysto-urethrograms were made, as it has been shown (Rossier and Bors, 1970) that retrograde urethrography, as originally proposed by Damanski (1961), did not provide reliable information in the spasticity of the external sphincter.

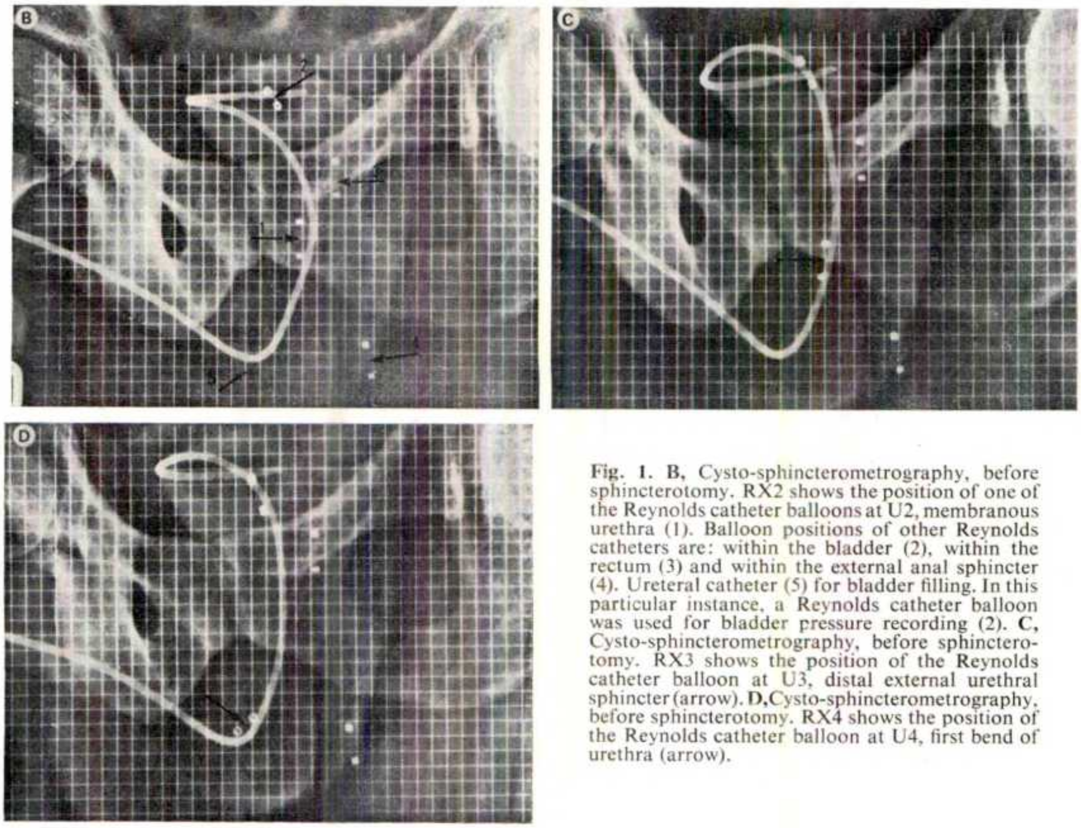

Fig. 1. **B,** Cysto-sphincterometrography, before sphincterotomy. RX2 shows the position of one of the Reynolds catheter balloons at U2, membranous urethra (1). Balloon positions of other Reynolds catheters are: within the bladder (2), within the rectum (3) and within the external anal sphincter (4). Ureteral catheter (5) for bladder filling. In this particular instance, a Reynolds catheter balloon was used for bladder pressure recording (2). **C,** Cysto-sphincterometrography, before sphincterotomy. RX3 shows the position of the Reynolds catheter balloon at U3, distal external urethral sphincter (arrow). **D,** Cysto-sphincterometrography, before sphincterotomy. RX4 shows the position of the Reynolds catheter balloon at U4, first bend of urethra (arrow).

Indication for Sphincterotomy

In the majority of cases, the indication for external sphincterotomy was based on the presence of significant residual urine, with or without reflux, with good opening of the bladder neck, and the demonstration of increased resistance at the external sphincter (Table I)[1]. One patient presented a bilateral urethral-scrotal fistula, with bilateral vas deferens reflux and marked spasticity of the external sphincter. One patient whose sphincter was too spastic when he was sitting, was able to urinate only when lying down.

Operative Technique

Sphincterotomy was performed with a Storz resectoscope mounted with a hook-shaped electrode, 5 mm in length. Two incisions 5 to 7 mm in depth were made, at 3 o'clock and at 9 o'clock, the length of the external sphincter, from the verumontanum, to the beginning of the bulbous urethra (Fig. 2), a distance of 15 to 20 mm (Kopsch, 1955). The muscular fibres of the external sphincter are easily visible and retract as they are sectioned, exposing the deeper layers (Fig. 3). The operation is often completely bloodless, especially if a mixed diathermic current is employed.

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[1] 65 cm H_2O "normal" average U3 pressure in 7 patients with upper motor neurone lesion whose bladder function stabilised spontaneously, without any urological intervention, versus 100 cm H_2O in our series of 17 patients who needed sphincterotomy (see Fig. 5).

Table I

Indications for Sphincterotomy in 28 Patients

Indication	Number	Paraplegics	Tetraplegics
Significant residual urine or micturition impossible	16	9	7
Significant residual urine and ureteral reflux	8	2	6
Reflux without residuum, spastic sphincter	2	2	...
Vas deferens reflux	1	1	...
Micturition possible only in recumbency	1	1	...

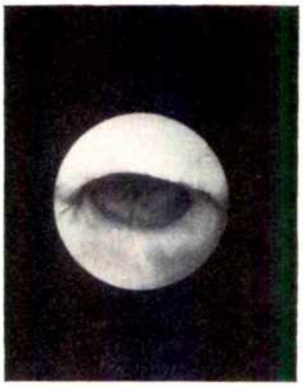

Fig. 2. Bilateral sphincterotomy, 6 weeks postoperatively: widened membranous urethra. Background: verumontanum and upper margin of the external urethral sphincter.

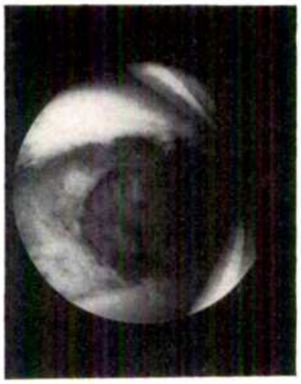

Fig. 3. Unilateral posterolateral sphincterotomy. From top to bottom: upper lip of the incised mucosa, sectioned fibres of the external urethral sphincter, deep fibres—still intact, lower lip of the mucosa.

The inferior border of the external sphincter must be carefully identified, since it is at this part that the sphincter exerts its maximum pressure, and incomplete section at this level may result in a significant residual obstruction. Likewise, accidental trauma to the corpus spongiosum is to be avoided, since excessive haemorrhage may result.

In the event of haemorrhage, we continued the operation as far as local visibility would permit. Postoperative control of haemorrhage was usually achieved by introduction of a large calibre (22 F) catheter.

Catheter drainage was continued postoperatively for 2 to 3 days. Depending on the volumes passed on micturition and the residual urine, drainage was continued for another 2 to 3 days, since postoperative oedema may hamper micturition for a while.

Results

(a) Clinical Observations

As it is too early to assess the results in the last 2 patients who underwent sphincterotomy for severe vesico-renal reflux *without residual* urine, estimation of clinical results in 26 of the 28 patients is presented.

Satisfactory results were eventually achieved in all of them: 24 had less than 50 ml residuum, 2 had between 50 and 100 ml.

Five patients underwent 2 sphincterotomies, and another underwent 3, before satisfactory results were achieved. However, favourable results were not always achieved by sphincterotomy alone (Table II).

A first group of 6 patients underwent initial bladder neck resection with either transient success or no success. Their bladder function was equilibrated with a secondary sphincterotomy.

In a second group of 9 patients, good bladder function was obtained with sphincterotomy alone. In 8 of these patients (documentation absent in the 9th), the preoperative voiding urethrogram showed patent bladder neck in 6, a wide bladder neck in the other 2.

A third group of 11 patients had unsatisfactory results with initial sphincterotomy. Before sphincterotomy, the voiding urethrogram showed a patent bladder neck in 3, a wide bladder neck in 2, a barely open bladder neck in 1; in the remaining 5, micturition was impossible, and the bladder neck did not open at all. With a subsequent transurethral bladder neck resection, results were satisfactory in all patients.

Table II

Sphincterotomy Results in 26 Patients

Results	Total	Paraplegics	Tetraplegics
Satisfactory results with sphincterotomy after initial failure of bladder neck resection	6	2	4
Satisfactory results: sphincterotomy alone	9	5	4
Satisfactory results with bladder neck resection after failure of initial sphincterotomy	11	6	5

It is interesting to note that in the second group of 9 patients, the average force of uninhibited contraction waves was nearly double that of the third group of 11 patients. In the second group the average force of contractions was 65 cm of water with an average membranous urethral resistance of 39 cm of water. In the third group the average force of contractions was 36 cm of water with an average membranous urethral resistance of 33 cm of water (Fig. 6). As bladder activity is known to be influenced by filling rate (Bors and Comarr, 1971), all recordings in this study were made at filling rate of 2·5 to 3 ml a minute.

(b) Manometry

We measured the urethral pressure at the external sphincter (U3) in 17 of our patients. After sphincterotomy (Fig. 4), the pressure was lowered from an average of 100 cm of water (range 75 to 120 cm of water), to an average of 33 cm of water (range 20 to 85 cm of water). Average reduction in pressure was 67% (Fig. 5).

Three patients had a preoperative pudendal nerve block with a consequent average lowering of pressure of 56% corresponding approximately to the figure of 50% found by Raz *et al.* (1971) and Tanagho and Miller (1970). These last authors, using a manometric technique similar to ours, attributed this decrease in pressure to a striated muscle component responsible for the closing of the urethra at rest.

Two cases seem to merit particular attention, since they show that it is possible, if necessary, to minimise or to graduate the extent of the sphincterotomy, especially in cases where preservation of urinary continence is desired.

The first patient underwent 3 successive sphincterotomies, of which the first 2 were relatively inextensive, through lack of experience with the technique. Prior to operation, the pressure was 95 cm of water, and fell to 75 cm of water after the first operation; to 60 cm of water after the second operation, and finally, to 45 cm of water after a third, definitive sphincterotomy.

The second patient bled to the extent that visibility was compromised and the operation had to be abandoned after a unilateral sphincterotomy had been achieved. Sphincter pressure fell from 95 cm of water to 55 cm of water; however, in spite of complementary bladder neck resection, significant residual urine persisted. A second sphincterotomy brought the residual urine to about 50 ml and reduced pressure from 55 cm of water to 30 cm of water.

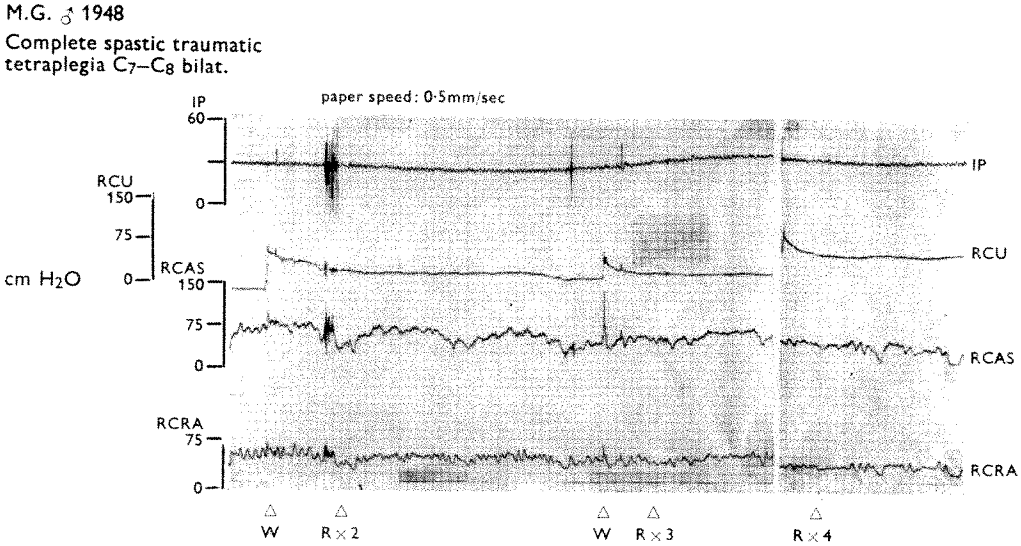

Fig. 4. Same patient as in Fig. 1, A, B, C and D. Cysto-sphincterometrography, 11 days after sphincterotomy. The recorded intra-urethral resistance (RCU) shows considerable decrease at U2, and U3, with no change at U4.

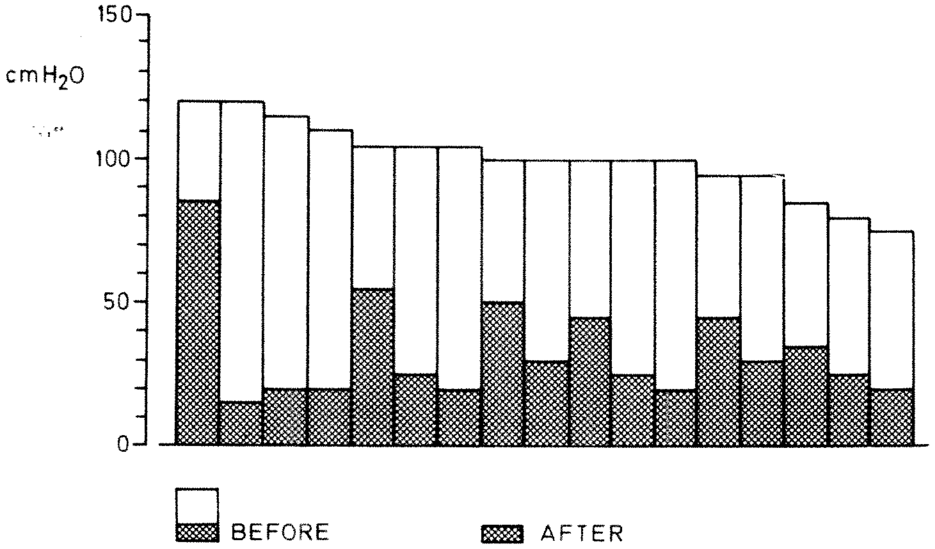

Fig. 5. Intra-urethral pressure at the level of the external urethral sphincter (U3), before and after sphincterotomy.

Complications

We experienced 4 operative haemorrhages, which necessitated abandoning the procedure in 2 cases. Haemorrhage was controlled in each case by the introduction of a large calibre catheter.

One patient presented 2 late postoperative haemorrhages on the 3rd and 7th postoperative days. Another patient went into hypovolemic shock on the 11th postoperative day, following massive haemorrhage. Haemostasis was achieved in both cases by introduction of a large calibre catheter.

(a) Urinary Tract Infection

In a total of 32 sphincterotomies in 26 patients whose urines were previously sterile, we observed 6 cases of significant transient postoperative bacteriuria, with no clinical symptoms.

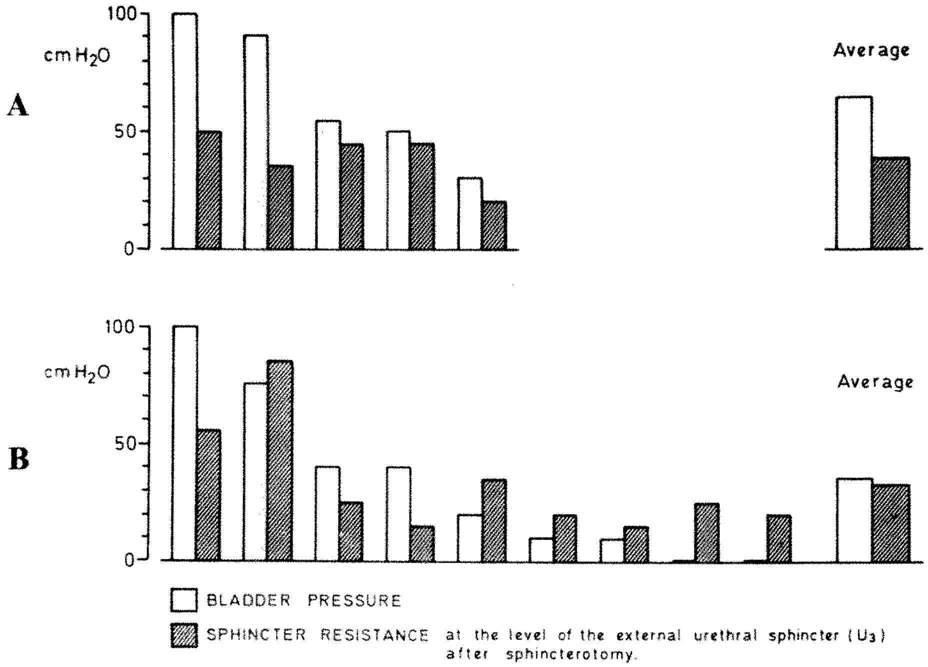

Fig. 6. Results after (A) sphincterotomy alone, and (B) after sphincterotomy followed by bladder neck resection.

(b) Perforation of the Urethra

In 40 sphincterotomies, Cosbie Ross *et al.* (1963) reported 3 cases of perineal extravasation of blood or irrigation fluid. We had no such experience.

(c) Incontinence

In the patients of this series, incontinence was not considered to be a complication, since most of the patients had to wear a collection apparatus, and had no control of micturition prior to operation.

The only patient with a lower motor neurone lesion, without anal or bulbo-cavernosus reflexes, with fibrillation of the external anal and urethral sphincters on EMG, was practically continent. As this patient had significant residual urine, we began with a bladder neck resection. This was unsuccessful, and in light of this failure and the high pressure at the external urethral sphincter, incidentally observed also by Murnaghan (1968), in patients with lower motor neurone lesions—we performed a sphincterotomy. The sphincter pressure, initially 80 cm of water, fell to 40 cm of water, and the residual volume previously in excess of 200 ml, fell to 50 ml. The patient, however, now manifests stress incontinence and has to wear a portable urinal.

Discussion

Transurethral sphincterotomy represents an alternative to pudendal nerve section. Technically the operation is easier and may be repeated without difficulty if necessary. There is usually no effect on erection, although 1 of our patients, unaffected by his first sphincterotomy, lost the capacity for erection following a second sphincterotomy. In contrast to pudendal neurectomy, sphincterotomy interrupts the submucosal elastic ring of the membranous urethra described by Gil Vernet (1953), Pennington and Lund (1960), as well as the circular smooth muscle fibres of the membranous urethra (Gil Vernet, 1968). In view of the sacral segmental interplay which exists not only between the detrusor and the striated muscles of the pelvic floor, but also between the pelvic floor muscles themselves (Bors, Comarr and Moulton, 1950; Bors, Rossier and Sullivan, 1962; Rossier and Bors, 1964), sphincterotomy may have an effect on a possible spastic component of the striated muscles of the pelvic floor and/or on the striated muscular fibres running from the external sphincter up to the bladder neck and trigone (Beneventi and Marshall, 1956; Bors, Comarr and Reingold, 1954; Manley, 1966; Sant, 1972; Young and Wesson, 1921).

Our results show that sphincterotomy reduced the pressure at the external sphincter to a greater extent than did pudendal nerve block (67% pressure in 17 cases versus 56% in 3 cases).

Clinical results, according to several authors (Bors and Comarr, 1954; Murnaghan, 1968; Cosbie Ross, 1956; Tsuji *et al.*, 1965), are satisfactory in about 70% of cases for these 2 types of operation. We achieved satisfactory results in 35% of cases with sphincterotomy alone and in 23% of cases with sphincterotomy after initial failure of bladder neck resection. Subsequent bladder neck resection resulted in satisfactory results in the last 11 patients in whom initial sphincterotomy failed. Thus, we eventually achieved 100% clinically satisfactory results. Retief (1970), Cosbie Ross (1968) and Tsuji *et al.* (1967), reported similar clinical results, between 80% and 100%.

Lack of synergism between the detrusor and the external sphincter is one of the most common causes of unbalanced bladder function in upper motor neurone lesions, *e.g.* contraction of the external sphincter occurring at the same time as detrusor voiding contractions are taking place. Preoperative voiding cysto-urethrograms are useful when a narrowing of the membranous urethra can be seen. Sphincterometrography findings bring out additional objective information concerning the degree of reflex activity displayed by the external sphincter. These findings are of a particular value as our multiple pressure recordings in the same patient have been shown to be almost reproducible when serial examinations were done under similar conditions. Both voiding urethrograms and sphincterometrography are examinations of a complementary value to each other. However, none of them did permit us to predict which patients would fall into either our second or our third groups, *i.e.* require bladder neck resection as well as sphincterotomy. Cystometrography is necessary to predict whether sphincterotomy alone or sphincterotomy associated with bladder neck resection will be required, particularly in patients with weak detrusor activity, as it has also been reported by Gibbon (1973), and in patients in whom the bladder neck does not open at all, or opens for the most part only in passive response to increase in intra-abdominal pressure (Credé manoeuvre). Transurethral bladder neck resection provides definitive anatomical bladder neck passage, and reduces the overall urethral resistance.

Spasticity of the striated muscle component of the bladder neck certainly plays a role in bladder outlet obstruction, as has been demonstrated by Bors *et al.* (1950) by pudendal nerve block, and by Cosbie Ross and Damanski (1953) by pudendal nerve section.

Our study shows that it is feasible to differentiate between patients who would benefit from sphincterotomy alone and those who require concomitant bladder neck resection. Our tests thus allow a more subtle adaptation of surgery to the requirements of the patient than that of Smith, Cook and Arrowsmith (1971) who suggested routine combination of the 2 procedures.

In most of our cases, the problem of incontinence was not a primary consideration, since satisfactory bladder emptying and sterile urine are 2 of the most vital elements to the survival of the paraplegic. In the presence of spasticity of the external urethral sphincter, and failure of the usual conservative type of management, 3 courses are open: indwelling catheter, pudendal nerve section, and sphincterotomy. The morbidity associated with the first one is such that some degree of urinary incontinence may be acceptable when a sphincterotomy may achieve satisfactory bladder emptying and conserve the integrity of the urinary tract.

Summary

Results are reported of transurethral sphincterotomy performed in para- and tetra-plegic patients. Indications and complications of the procedure are discussed.

Six patients required multiple sphincterotomies before obtaining satisfactory bladder function. After failure of the initial sphincterotomy 11 patients required additional bladder neck resection.

After sphincterotomy, with or without supplementary bladder neck resection, the volume of residual urine remained between 50 and 100 ml in 2 patients, and fell below 50 ml in 24.

A technique for recording pressure within the membranous urethra via a special balloon catheter allowed objective measurement of the results of the procedure. At the level of the distal part of the external urethral sphincter, just at the beginning of the bulbous urethra, an average reduction in pressure of the order of 67% was found postoperatively.

It has been found that the power of the bladder contraction determines which patients benefit from sphincterotomy alone and those who require concomitant bladder neck resection.

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Incomplete Urethral Duplication and Urinary Retention

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Duplication of the urethra is a rare abnormality. The usual presenting features are infection (often venereal), double stream, incontinence and chordee (Gross and Moore, 1950). The condition can be symptomless. Urinary retention is rarely associated with urethral duplication (Gross and Moore, 1950). This paper describes 3 cases of incomplete urethral duplication with urinary retention.

Case Reports

1. D. T. An 8-year-old boy was admitted with his third attack of acute retention. Between these episodes he had had no symptoms. His genitalia appeared normal and there were no abnormal neurological signs. Urography showed no abnormality in the upper urinary tract. A cystoscope was introduced without difficulty. No abnormality was seen in his urethra but the bladder was trabeculated. An expression urethrogram showed what was thought to be a urethral diverticulum (Fig. 1).

At operation an apparently normal urethra was exposed through the perineum. On incising the urethra longitudinally it was found to be divided into dorsal and ventral channels by a septum approximately 1·5 cm long. The septum was excised and the urethra closed. The boy has since remained free of symptoms.

2. E. F. This boy developed right epididymitis at 5 years of age. Urography showed a hypertrophied left kidney and a grossly dilated right ureter (the kidney was not seen). His external meatus appeared normal but would not admit a fine catheter. A cysto-urethrogram obtained by filling the bladder through a suprapubic catheter showed a trabeculated bladder, gross right-sided reflux both into the dilated ureter and via a persistent mesonephric duct to the right epididymis, and a urethral duplication from the region of the verumontanum to the glans (Fig. 2). On 2 occasions while in the ward he developed acute retention.

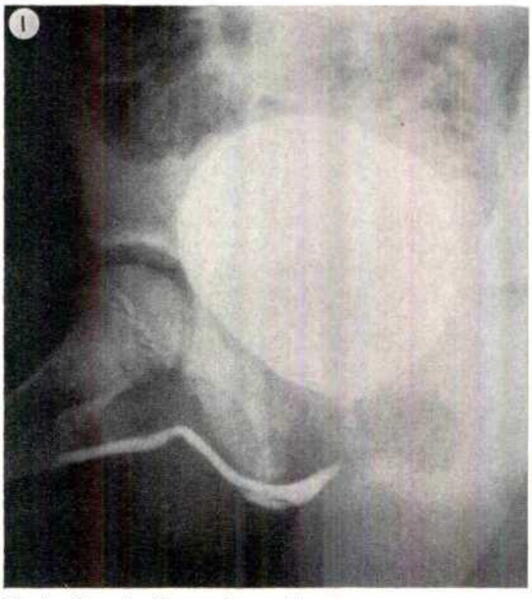

Fig. 1 Case 1. Expression urethrogram

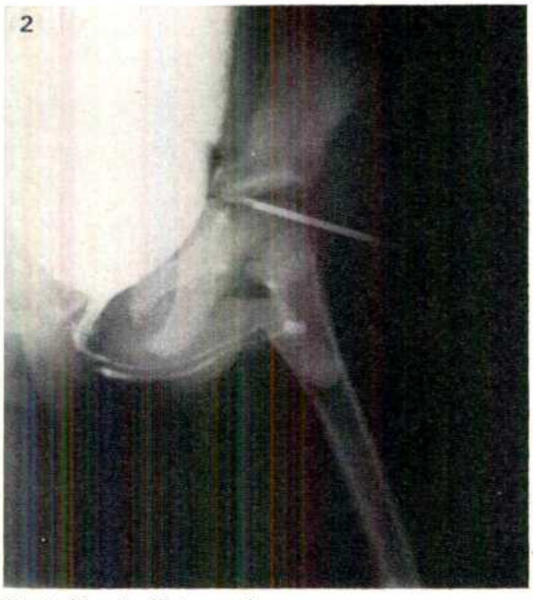

Fig. 2 Case 2. Cysto-urethrogram

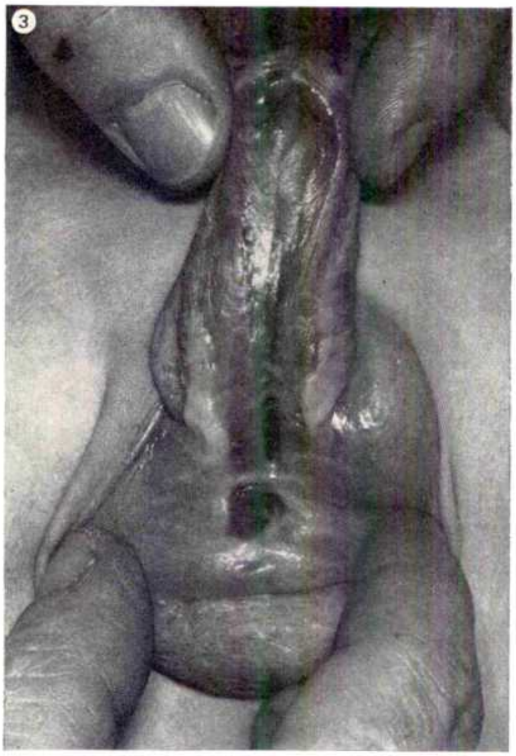

Fig 3 Case 2. First stage urethroplasty

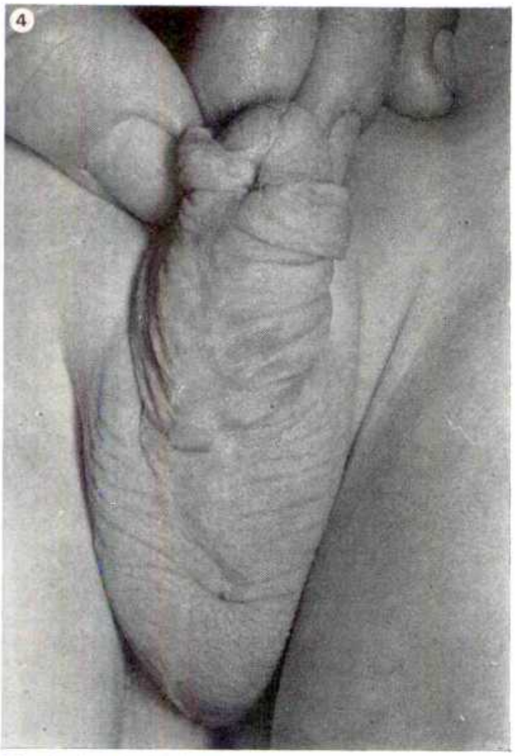

Fig. 4 Case 2. Following reconstruction of the urethra

The normally sited meatus was the opening of the narrow dorsal channel, whereas the ventral urethra, which was of normal calibre, opened through a separate tiny orifice on the glans penis. At operation the ventral urethra was opened longitudinally and the septum between it and the dorsal urethra was divided. A perineal skin flap was fashioned and sutured to the posterior wall of the posterior urethra creating a perineal urethrostomy. The appearance of the penis after this procedure is shown in Figure 3. Subsequently the functionless right kidney and its ureter were removed and the urethra reconstructed to establish a terminal meatus (Fig. 4).

3. D. R. This boy was seen at 4 years of age having leaked urine continuously from birth. He had a distended bladder and a pinhole urethral meatus in the normal position. In addition he had Marfan's syndrome and radiography showed a spina bifida of T10 and T11. There were no abnormal neurological signs and no myelographic evidence of spinal cord compression. His renal function was impaired and his upper tracts grossly dilated (Fig. 5).

Following dilatation of the external meatus it was possible to pass only a very fine catheter into the bladder. A cysto-urethrogram showed a trabeculated bladder and a duplication of the penile urethra (Fig. 6). The double urethra, which had a single meatus, was laid open through a ventral incision, thus forming a hypospadiac urethral orifice. For the following 3 years he passed urine with a good stream, but also leaked urine if his bladder became full and was not able to stay dry for longer than 1 hour. His bladder remained impalpable. At the age of 8 a urethroplasty was performed to give him a terminal meatus, but he was unable to empty his bladder adequately. The urethroplasty was undone to convert him back to his previous state. Seven years later his urinary symptoms were unchanged. His bladder was not palpable. He developed a scoliosis but there were no abnormal neurological signs in his legs or perineum.

Comment

The embryogenesis of urethral duplication is open to conjecture and may not be the same in different types of duplication. Continued forward splitting of the urorectal septum (Slotkin and Mercer, 1953; Wilson, 1971) could account for duplication of the bladder and urethra but not of the urethra alone (Mogg, 1968) or in association with ectopic anus (Bramwit and Ziter, 1970).

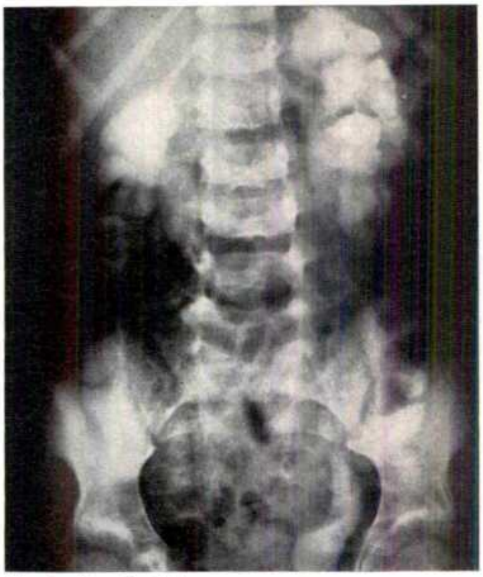

Fig. 5 Case 3. Intravenous urogram

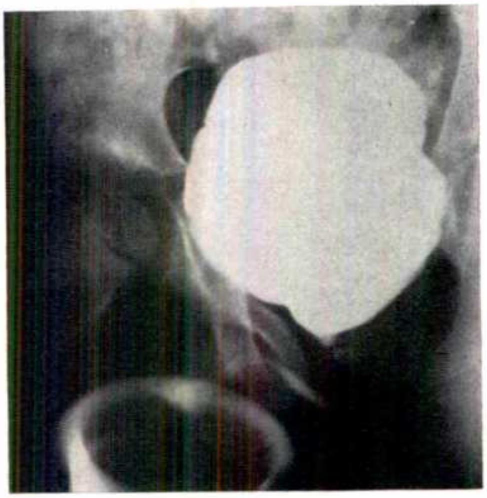

Fig. 6 Case 3. Cysto-urethrogram

Incomplete duplication may be caused by bifurcation of the urethral gutter (Mogg, 1968; Bramwit and Ziter, 1970) or infolding of lateral mesodermal elements into the urethral anlage (Tripathi and Dick, 1969). In urethral duplication, whether complete or incomplete, one urethra is usually of normal calibre. Urinary retention may occur if neither channel is of adequate calibre or if an accessory channel with a blind distal end compresses the main channel during attempted micturition. The latter was the mechanism in a case reported by Higgins, Williams and Nash (1951) and both factors were present in Liban's case (Liban, 1952). In the present report neither Case 2 nor Case 3 had a urethra of normal calibre throughout. In Case 3 retention may have been partly due to detrusor weakness as the urethra proximal to the bifurcation was not dilated. The mechanism of retention in Case 1 is not clear. Minor trauma may have produced sufficient oedema of the membrane separating the 2 channels for it to obstruct the urethra.

A number of different operations have been devised to correct urethral duplication. These include obliteration of 1 channel by diathermy coagulation or injection of sclerosants, division of the septum separating the 2 urethras, total excision of the accessory urethra and marsupialisation of both channels followed by urethroplasty (Gross and Moore, 1950; Atherton, Atherton and Sexter, 1967; Tripathi and Dick, 1969; Schmidt, 1971). Total excision has proved its worth in dorsal duplication but is inapplicable if the main urethra is stenosed as in Cases 2 and 3. Two patients (Cases 2 and 3) were treated by laying open both channels on the ventral aspect of the penis. Following this operation the ventrum of the penis consisted of urethral epithelium derived from both channels. At subsequent urethroplasty the new urethra was constructed with this epithelium and not from penile skin as in the repair of congenital hypospadias. This method is recommended for the correction of an anterior incomplete duplication if there is any doubt concerning the adequacy of the main urethral channel.

Summary

Three boys with incomplete urethral duplication and urinary retention are reported.

The mechanism of retention is discussed and operative correction by marsupialisation of both channels and subsequent urethroplasty described.

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The Pressure Exerted by the External Sphincter of the Urethra when its Motor Nerve Fibres are Stimulated Electrically

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Attempts have been made, with some success, to treat urinary incontinence by electrical stimulation of nerves or muscles. Such stimulation is done either through anal or vaginal electrodes (Alexander *et al.*, 1970; Hopkinson, 1972), or by an implant whose electrodes lie near the pudendal nerves (Caldwell, 1967; Caldwell *et al.*, 1968*a* and *b*). Early users of such devices seem to have supposed that they directly stimulate motor nerve fibres innervating the external urethral sphincter. However, Collins (1972) has given good grounds for believing that the anal devices do not do this, and our observations support his conclusion and extend it to the vaginal devices. Even for the implants, the hypothesis that the beneficial effects are mainly due to direct stimulation of motor nerve fibres is not yet supported by any published evidence.

Though it may be uncertain whether motor fibres innervating the external sphincter are effectively stimulated by the devices now in clinical use, they can certainly be stimulated by electrodes implanted in contact with sacral ventral roots of the cauda equina in experimental animals, and such implants have been suggested as of possible clinical value in man (Brindley, 1972). It therefore seemed useful to examine the behaviour of the human external sphincter under electrical stimulation of its motor nerve fibres. We experimented on ourselves as subjects (male, aged 47, 28 and 29 years) on one male volunteer aged 31, and on two female volunteers aged 31 and 24. Experiments involving catheterisation were done only on ourselves.

Direct and Reflex Activation of Pudendally Innervated Muscles by Anal Plug Electrodes

The anal continence aid of Hopkinson and Lightwood (1967) as made by Cardiac Recorders Ltd manifestly does not stimulate *all* the motor fibres of the pudendal nerves, for when it is in place and its stimulator turned to full strength, voluntary contraction of the perineal muscles is possible and appears completely normal. Voluntary micturition in all our subjects is unimpeded or nearly so by this device when fully switched on, as Alexander *et al.* (1970) noted for their vaginal device (and we confirm), and as we find also for the vaginal device of de Soldenhoff and McDonnell (1969) made by Vitalograph Ltd.

Probably the Hopkinson-Lightwood device does not stimulate any motor fibres of the pudendal nerve, unless perhaps some that innervate the anal sphincter and levator ani, for when we delivered through its plug shocks from a Devices Digitimer equal in amplitude and duration to the strongest that the Hopkinson-Lightwood stimulator would deliver (0·9 msec and 7·0 V on load) but at lower frequency (12 pulses/sec instead of 155 pulses/sec), no electromyographic activity was recorded by stainless steel wire electrodes (12 mm in length) in the ischiocavernosus muscles. The strength of stimulus had to be trebled or quadrupled before any electromyographic responses could be detected. They were then purely reflex (latency 65 msec) in 2 out of 3 experiments and both reflex and direct (latencies 70 and 5 msec) in the third.

When we put stimuli of even greater strength through a Hopkinson-Lightwood plug (up to

40 V at 12, 24 or 54 pulses/sec, using a Devices Digitimer and supplementary output amplifier), we were able to cause some slight sensation in the scrotum and penis. Presumably some sensory fibres of the pudendal nerves were then being stimulated, but this referred sensation was experienced only when the stimuli were strong enough to cause severe pain around the anus. During trains of stimuli of this strength, voluntary contraction of the perineal muscles was still possible, so evidently even then not all the motor fibres of the pudendal nerves were being stimulated. We therefore designed the modified anal plug shown in Figure 1, C and D. It has 2 internal electrodes, arranged to lie as near as possible to the pudendal nerves, and 2 external electrodes which are much larger than the single external electrode of the Hopkinson-Lightwood plug. With the plug of Figure 1, C and D, a state in which attempted voluntary perineal contraction caused no externally visible movement could be achieved by means of stimuli that caused only slight or moderate pain, or sometimes even no pain. Whether painful or not, the sensations accompanying the state in which attempted voluntary contraction of the perineum was ineffective were always strong, and always contained a component referred to the scrotum and penis in men, and to the vulva in women. Figure 2 shows that with this device the ischiocavernosus muscles can be activated by direct stimulation of their motor nerve fibres, and that the ischiocavernosus muscle of the right or left side can be activated alone. Figure 3 shows that the external sphincter of the urethra also can be activated by direct stimulation of its motor nerve fibres through the anal plug of Figure 1, C and D.

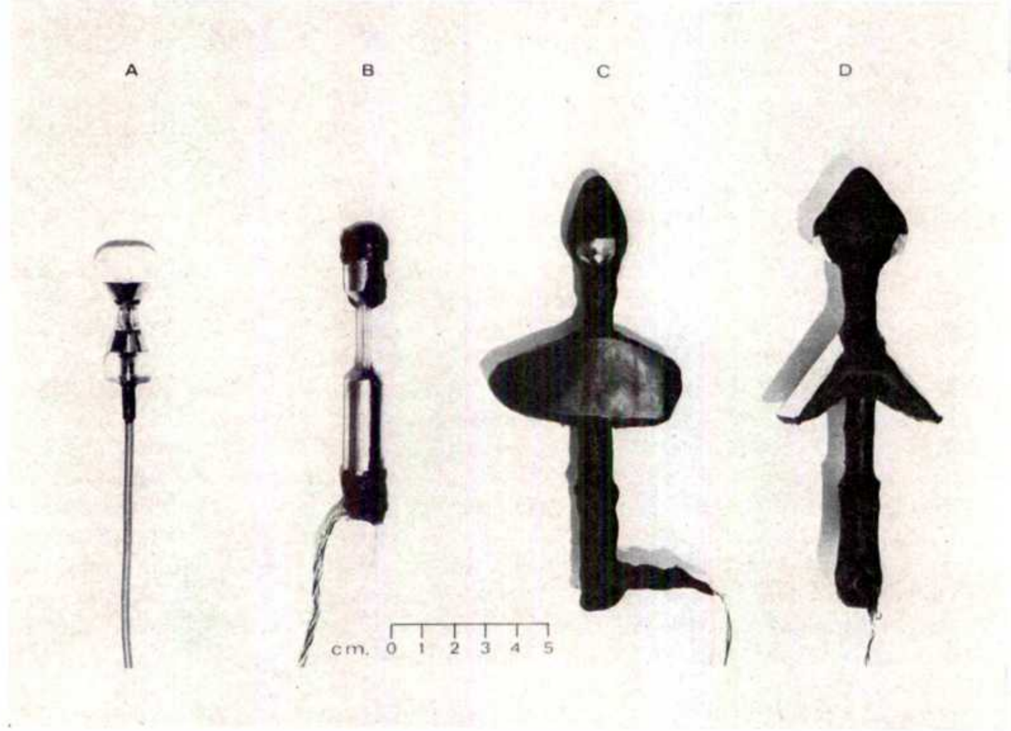

Fig. 1. The electrode-bearing anal plugs used in the experiments. (A) is the smallest size of Hopkinson-Lightwood plug. (B) shows the plug (described in the test) which was designed for measuring contractions of the anal sphincter as well as provoking them. (C) and (D) show lateral and anterior views of the plug that we designed specially to give the best possible stimulation of the pudendal nerves and the least possible anal sensation. The 2 active electrodes (cathodes during the 0·5 msec high-current phase of our asymmetrical biphasic pulses) lie laterally near the junction of anal canal and rectum. The 2 large indifferent electrodes make contact partly with anal skin and partly (through electrode jelly) with the inner surfaces of the buttocks.

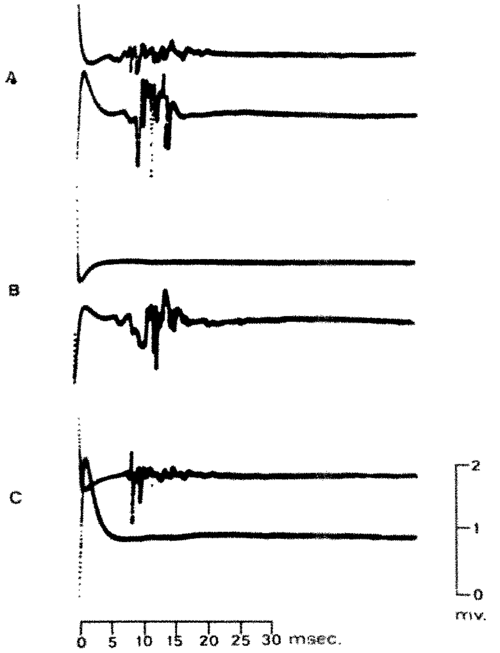

Fig. 2. Electrical responses of the ischiocavernosus muscles, recorded with bipolar Adrian-Bronk needles inserted into them. In each record the upper trace shows the left muscle and the lower the right. In (A) the stimulus was a single shock delivered between both inner and both outer electrodes of the plug of Figure 1 (C) and (D). In (B) it was delivered between the right inner and the right outer electrode, and in (C) between the left inner and the left outer. The latencies of the responses are clearly too short for them to be reflex. Subject M. D. C.

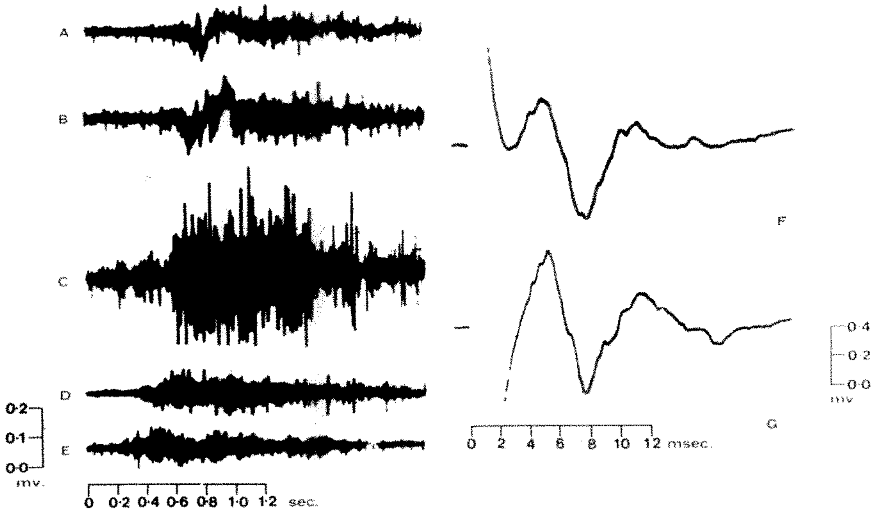

Fig. 3. Electromyograms recorded with a urethral catheter bearing 5 pairs of platinum wire electrodes of surface about 1 mm², each pair 16 mm from the next pair. Records (A) to (E) show voluntary contractions of the pelvic floor muscles (evidently, as expected, including the external sphincter of the urethra). Much more activity is recorded by pair (C), which was 165 mm from the meatus, than by any other pair. When the catheter was withdrawn by 16 mm, maximal activity shifted to pair (B). This part of the Figure merely shows that such intra-urethral electrodes can distinguish the external sphincter from other striated muscle in the neighbourhood. Records (F) and (G) show, on a faster time-base, responses recorded with pair (C) to single shocks delivered between both internal and both external electrodes of the plug of Figure 1 (C) and (D). (F) and (G) were made with stimuli of opposite polarity. The large stimulus-artifacts reverse their polarity between (F) and (G), but the down-going wave at 7·5 msec and the upgoing wave at 5·5 msec do not. They are therefore (as their relation to strength of stimulus also showed) not parts of the stimulus-artifact, but responses of the muscle. Their short latency shows that they cannot be reflex. Subject G. S. B.

Figures 2 and 3 illustrate only direct responses. Reflex responses were also sometimes visible in the electromyograms, but inconstantly. Their latencies were sometimes around 10 msec, as would be expected of H-reflexes, but more often they were around 60 msec, as might be expected of reflex responses to stimulation of cutaneous fibres.

In the course of the present experiments we used several different criteria to decide whether an electrically induced contraction was maximal, *i.e.* involved all motor units in the muscle. One is mentioned above, *i.e.* whether attempted voluntary contraction of the perineal muscles causes any externally visible movement. This criterion could be subdivided: we could look for retraction of the penis, or for indrawing of the anus seen as movement of the anal plug. Other criteria used movements that could not, or could not easily, be seen directly. We sometimes examined contractions of the anal or urethral sphincter as detected by manometric devices (see pp. 443 and 444), or, in women, felt contractions of the urethral sphincter through the anterior vaginal wall. Whatever muscle was examined, we could use, as criterion of maximality, either its failure to take part in attempted voluntary contraction or its failure to respond to further increase in the strength of the stimulus. The experiments on producing retention of urine (see below, p. 445) provided, for the external sphincter of the urethra, a criterion of a different kind: if at a certain strength of shocks at a given frequency the subject could expel urine, and at a greater strength at the same frequency he could produce the sensation of impending micturition but could not expel urine, we inferred that the external sphincter of the urethra could not have been contracting maximally in response to shocks of the first strength.

We found that all criteria of maximality that we tried on any one occasion were reached at roughly similar strengths of stimulus. The strength needed for the urethral sphincter was greater than that needed for the ischiocavernosus muscle by from 5% to 20%, and that needed for the levator ani was on most trials intermediate. Evidently the motor fibres of the pudendal nerves innervating different muscles do not differ greatly in size.

Fatigue of the Anal Sphincter Under Electrical Stimulation

Our main concern in this paper is with the external sphincter of the urethra. Sphincterometers such as those of Simons (1936), Enhörning (1961) and Emanuel (1963) record the pressure exerted by this muscle, but it is difficult to adapt them so as to measure accurately the sustained pressures exerted by the muscle during prolonged electrical stimulation, and it is principally these pressures that must be known if we are to design the best possible sphincter stimulator. We therefore concentrated, in experimenting on the urethral sphincter, on developing a technique that measures sustained pressures accurately; but this technique is not without risk (of infection), and is not suitable for measuring changes, other than very slow ones (see below, p. 443). Faster changes, however, are also of interest, so we examined them by simple and safe experiments on the anal sphincter, expecting that the behaviour of the anal sphincter would give us a rough general idea of the way in which the urethral sphincter was likely to behave.

We made an anal plug (Fig. 1, B) similar to that of Hopkinson and Lightwood except that the isthmus between the electrodes was longer (20 mm instead of 10 mm), narrower (5 mm external diameter), and made of silicone rubber tube. Within this silicone rubber tube lay a stainless steel rod, which was rigidly fixed to the rectal knob and external cone and prevented them from moving in relation to each other. The rod was not attached to the silicone rubber tube that loosely surrounded it. The lumen of the tube was connected to a hydrostatic manometer. The system was calibrated either by enclosing the whole anal plug in a pressure-chamber or by wrapping a small specially made sphygmomanometer cuff round the isthmus. Neither mode of calibration closely imitates what the sphincter does to the isthmus, and they give different absolute calibration, but both show a linear relation between applied pressure and manometer reading. Thus relative pressures in Figure 4 can be trusted, though absolute values are very uncertain.

Figure 4 shows the time-course of pressure exerted by the sphincter during 10 minutes of continuous maximal stimulation at various frequencies, and during the 5 minutes after ceasing to stimulate. On this occasion no attempt was made to read the manometer until 30 seconds after the beginning of stimulation; but in other similar experiments it was noted that during the first few seconds the pressure recorded was highest for 54 pulses/sec and lowest for 12 pulses/sec. The curves typically cross between about the 5th and the 10th second. We can say that the sphincter fatigues much faster at high than at low frequencies of stimulation. Its immediate relaxation when the train of shocks ceases involves a greater fall in pressure when the frequency of the train is low, than when it is high, and the pressure in the thoroughly fatigued state under stimulation exceeds the pressure in the resting relaxed state by more at 12 pulses/sec than at 24, and by more at 24 pulses/sec than at 54. Thus for producing the most powerful possible sustained contraction of the anal sphincter by stimulation of motor nerve fibres, 12 pulses/sec is a better frequency than 24 or 54. Reduction of frequency below 12 pulses/sec is probably not useful, because the contraction, which already at 12 pulses/sec shows a small ripple that can be seen and felt, becomes at lower frequencies very oscillatory, *i.e.* a train of twitches rather than a tetanus is produced.

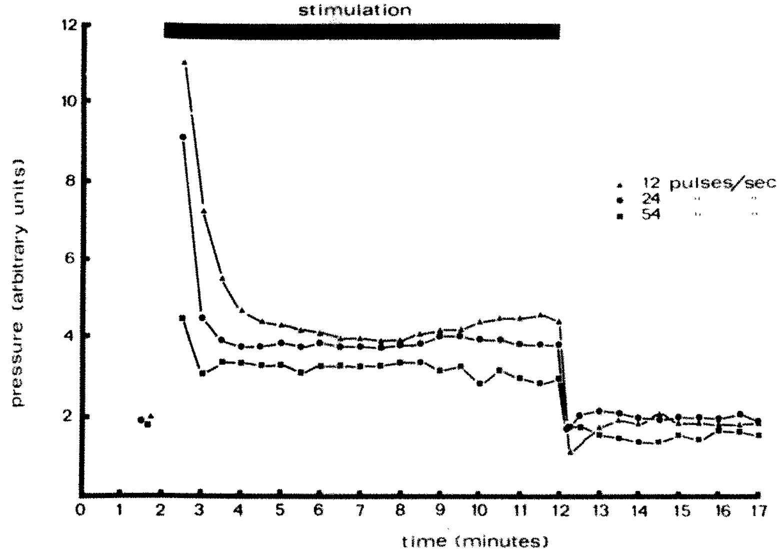

Fig. 4. The time-course of pressure exerted by the anal sphincter during 10 minutes of maximal stimulation, and during the 5 minutes after ceasing to stimulate. The pressure immediately after beginning to stimulate always exceeded 14 units at any frequency, and was typically a little higher at high than at low frequencies, but fatigue during the first half-minute was much greater at high frequencies, so that the first formal reading in the experiment illustrated (which is typical) shows a much greater value at low than at high frequencies. Comments on other features of the experiment are made in the text. Subject G. S. B.

The Retrograde Pressure Withstood by the External Sphincter of the Urethra

To estimate the pressure exerted by the external sphincter on the urethra during prolonged electrical stimulation of the motor fibres of the pudendal nerves, we inserted a catheter into the distal 7 cm of the urethra, obtained a watertight seal by means of either tightly wound adhesive tape or a little pneumatic cuff round the penis, injected sterile water at known rates through the catheter into the bladder by means of a roller pump or a syringe, and measured the pressures developed with a mercury manometer connected to a branch tube that left the catheter close to the external meatus. The bladder was never allowed to become uncomfortably full.

With the sphincter voluntarily contracted, or during the first 15 seconds of maximal stimulation through the anal plug of Figure 1, B and C, the pressure reached 180 mm Hg with very small (probably zero) flow. We do not know by how much this pressure might be exceeded without breaking down the resistance of the sphincter; we quickly stopped the roller pump to avoid risk of damage to the apparatus or the subject. With the sphincter voluntarily relaxed, water flowed into the bladder at rates between 13 and 105 ml/min at pressures between 55 and 110 mm Hg. At any rate of flow, the pressure fluctuated over much of this range unpredictably. As expected, the pressure tended to be greater at high than at low flows, but the variation of pressure with flow was smaller than its unpredictable fluctuation. We think that most of the unpredictable fluctuation was due to the subject's failure to relax the sphincter consistently under these conditions.

During prolonged maximal stimulation through the anal plug of Figure 1, more consistent pressure-flow relations were obtained, and so were they in the relaxed state during the first minute after ceasing such stimulation. During this minute we found relaxation especially easy. Some of this ease of relaxation is doubtless due to the fatigued state of the sphincter, but this may not be its sole cause.

Our procedure with the second and third subjects tested (M. D. C., D. N. R.) was as follows. First the urethra distal to the sphincter was filled by means of the roller pump until a pressure of about 60 mm Hg was reached. The pump was then stopped. The pressure then typically remained stable within ± 5 mm Hg unless the subject made a voluntary contraction of the perineal muscles (in which case it rose gently). The subject next switched on the anal plug stimulator, and turned the knob that increased the amplitude of the stimulus until either the pelvic floor contraction appeared to be maximal or the sensation was too unpleasant for further increase to be tolerated. In the latter case we always found that if the subject waited for a few seconds or tens of seconds to become adapted to the stimulus, he could then tolerate a further increase. During most of the process of increasing the amplitude of the stimulus, each step caused a sudden rise in the manometer reading followed by a slower fall. Above a certain amplitude, however, further increase had no effect on the manometer reading, or none exceeding 2 mm Hg. We took this as our principal criterion that the stimulus was maximal (though we usually also looked to see whether attempted contraction of the perineal muscles caused movement of the penis or anal plug). Our principal criterion may really represent stimulation of all the fibres to the bulbospongiosus muscle rather than all the fibres to the external sphincter, but this distinction is probably not of great importance. We allowed maximal stimulation to continue for 3 minutes before beginning to measure the relation between flow and pressure. About another 3 minutes of maximal stimulation were usually required to complete the measurements, which consisted of manometer readings for each of 3 or 4 previously assigned settings of the roller pump. Our roller pump gave flows that were independent of back-pressure within 1% over the range met in the experiments. Analogy with the anal sphincter (Fig. 4) suggested that 3 minutes would probably be long enough for fatigue to be nearly complete, and we noticed no tendency for the opening pressures to rise or fall with time. The measurements on G. S. B. were made by an inferior method, injecting by hand with a syringe instead of with a roller pump, but we did not feel justified in repeating them after we had improved the technique.

Table I shows, for the 3 subjects, the relation between flow and pressure for maximal stimulation at 12 and 54 pulses/sec and in the relaxed state during the first minute after ceasing to stimulate. The low pressures required to produce the observed flows in the relaxed state after fatigue show that the opening pressure for retrograde flow through the internal sphincter is low, as has been observed before (*e.g.* Baumann, 1955). Its exact value therefore does not need to be considered in interpreting the measurements made under stimulation; we can say that the opening pressure for retrograde flow through the external sphincter is roughly 120 mm Hg during prolonged maximal stimulation at 12 pulses/ sec, and roughly 90 mm Hg during prolonged maximal stimulation at 54 pulses/sec. Thus the effect of frequency of stimulation is of the same kind as for the anal sphincter.

For the external sphincter, which is generally supposed to act by directly squeezing the urethra, the opening pressure is likely to be the same in both directions. This would not apply to the internal sphincter, where Baumann (1955) reported a difference in opening pressure for the two directions and argued from the difference that closure of the internal sphincter was a passive process and opening during micturition an active one—a conclusion that has received support from evidence of very different kinds (Lapides, 1958; Woodburne, 1960).

Table I

		Pressures in mm Hg		
Subject	ml/min	Stimulated 12/sec	Stimulated 54/sec	Relaxed Immediately after Stimulation
M. D. C.	36·5	108, 120	90, 85	55, 55
	64	120, 128	100, 90	59, 59
	105	128, 135	110, 100	66, 64
D. N. R.	12·0	140, 115	95	65
	36·5	138, 120	95	70
	63	144, 140	110	75
	103	159, 148	120	95
G. S. B.	8	110		
	16		90	
	40	120	110	

The Production of Retention of Urine by Stimulation of Motor Fibres to the External Urethral Sphincter

In contrast to the easy micturition during the strongest stimulation that the Hopkinson-Lightwood and (in women) Alexander-Rowan and de Soldenhoff-McDonnell devices can deliver, we found that during prolonged maximal stimulation at 12 or 24 pulses/sec through the anal plug of Figure 1, C and D all subjects were totally unable to expel any urine, even when the sphincter had been fatigued by 5 minutes (for ourselves and one female subject also 10 minutes, and on one occasion 40 minutes) of maximal stimulation. We have to consider whether this was because the external sphincter was so firmly closed that, with the internal sphincter open, contractions of the bladder and abdominal muscles were inadequate to overcome it, or whether it might have some other cause.

We guessed, even before we had tried it, that very strong sensations from the anal and perineal region would make it difficult to initiate contraction of the detrusor and opening of the internal sphincter. This proved to be so for all subjects. We believe, however, that we and our volunteers were able to overcome this difficulty. The evidence is as follows:

1. Trains of pulses of current passed between the 2 external electrodes of the plug of Figure 1, C and D, or between 1 external electrode and the internal electrode of the same side, can produce sensations just as strong and uncomfortable as those produced by normal use of the plug, without causing maximal contraction of the pudendally innervated muscles bilaterally (in the second case they produce it unilaterally, in the first case not at all). Such trains do not prevent micturition, though all subjects needed practice to learn the art of starting in the presence of the strong sensation that they cause.

2. If we stimulated between both internal and both external electrodes with strengths of shock that at 12 pulses/sec gave clearly maximal contractions of the observable pudendally innervated muscles, but used frequencies below 7 pulses/sec, micturition was not prevented, though the rate of flow was decreased. At 1 pulse/sec, such stimulation caused regular interruptions in the flow, which were total in women and only partial in men (doubtless because the urethra distal to the sphincter is a larger reservoir in men).

3. During maximal stimulation at 12 or 24 pulses/sec, though no micturition was possible, subjects could learn to produce the sensation of impending micturition. If when this sensation was present the stimulator was switched off, urine came out of the meatus with a delay of less than $\frac{1}{2}$ second. We infer that the sensation of impending micturition can be a reliable index of opening of the bladder neck and contraction of the detrusor, and that with practice these events can be caused to occur during prolonged maximal stimulation of the pudendal nerves, but nevertheless no urine can be forced past the contracted (though fatigued) external sphincter.

Two of us found that, when we had learned to produce sensations of impending micturition during maximal stimulation at 12 or 24 pulses/sec, it was still difficult (G. S. B.) or impossible (M. D. C.) to produce them during stimulation at 54 pulses/sec. D. N. R. did not have this difficulty, and subjects other than the authors did not attempt micturition during maximal stimulation at 54 pulses/sec. Those who attempted it and succeeded in getting sensations of impending micturition (D. N. R., G. S. B.) also succeeded, on some trials, in forcing some urine past the contracted but fatigued sphincter. Evidently, at least in us, the pressure exerted by the sphincter fatigued at 54 pulses/sec is not quite sufficient for continence; that exerted by the sphincter fatigued at 12 or 24 pulses/sec is sufficient, but cannot be so by a large margin, if the retrograde flow experiment is a fair guide.

The Degree of Continence Maintained by the Internal Sphincter when the External Sphincter is Paralysed

On one of us (G. S. B.) a bilateral pudendal nerve block was performed at the level of the ischial spines during a water diuresis. The block was complete as judged by cutaneous anaesthesia and by the failure of attempted voluntary contraction of perineal muscles to cause any externally visible movement.

In this state, with a full bladder, it was possible to blow up a column of mercury by mouth to 110 mm Hg without any leakage of urine. Voluntary micturition was possible. We recorded its time-course twice. On the first occasion, pudendal anaesthesia was complete. The speed with which 260 ml of urine was expelled was only about half of the normal speed for the subject. On the second occasion (375 ml expelled) pudendal anaesthesia was no longer quite complete. The speed of emptying was then about three-quarters of normal. We would tentatively suggest that the slow emptying may be due to the loss of the urethro-vesical reflex that Barrington (1931) asserted (on obscure evidence; the paper of Guyon (1900) referred to gives none) to exist in the cat. We know of no previous evidence bearing on the question whether man has such a reflex.

After we had done this experiment, we read that it had been done before (Emmett, Daut and Dunn, 1948; Lapides, Gray and Rawling, 1955). We report our replication, because the earlier experimenters gave no quantitative statement of the intra-abdominal pressure that could be sustained by the internal sphincter, and did not mention slowing of micturition.

Discussion

The "internal sphincter", whatever may be its anatomical nature, is normally sufficient for continence, as the experiment on pudendal block shows.

The principal new conclusion from our experiments is that the normal external sphincter can, under electrical stimulation at 12 pulses/sec, imitate the functions of the internal sphincter, *i.e.* maintain continence against contractions of the detrusor or rise of intra-abdominal pressure or both, and sustain its contraction at least for many minutes.

If this new knowledge is to be used in a therapeutic device, a means of stimulating the motor fibres to the sphincter without causing severe discomfort is needed. Though our anal plug is doubtless not quite the best that can be designed, we are confident that it is not very far from optimal, and that no anal plug will stimulate all the motor fibres of the pudendal nerves without causing local sensations too disturbing to be tolerated hour after hour by patients pursuing their ordinary occupations. If stimulation of motor fibres of the pudendal nerves by anal plugs is to have a clinical application, it must be one where the discomfort needs to be tolerated for no more than a few minutes. Such an application might be in a test for assessing the function of the pudendally innervated muscles in an individual patient—for example for deciding whether the insertion of an implant of the kind introduced by Caldwell, or one intended to stimulate the S3 and S4 ventral roots (Brindley, 1972), would be justified.

Though we are sure that prolonged stimulation of all or most of the motor fibres of the pudendal nerves cannot in patients with intact sensory pathways be achieved through anal electrodes without an unacceptable degree of discomfort, it remains possible that it might be achieved with vaginal electrodes. The vaginal device of de Soldenhoff and McDonnell is very far from achieving it. That of Alexander and Rowan comes nearer, since its electrodes are better placed in relation to the relevant branches of the pudendal nerves, but with its own stimulator, as made by Devices Implants Ltd, it fails to produce maximal contraction of the relevant muscles and hardly obstructs micturition. We find that the pessary of Alexander and Rowan driven by our powerful stimulator at 20 pulses/sec also fails to obstruct micturition, at the greatest strength of stimulus that the subjects can tolerate.

In a further attempt to achieve better discrimination between the branches of the pudendal nerve that innervate the closing muscles and irrelevant sensory fibres, we tried stimulating between the electrodes of an Alexander-Rowan pessary and the internal electrodes of our plug of Figure 1, C and D. If the vaginal electrodes were made cathodes, the strongest tolerable stimulus failed to obstruct micturition. If the anal electrodes were made cathodes, micturition could be obstructed. The stimulus needed to obstruct it was in both our subjects slightly, but only slightly, less uncomfortable than that between internal and external anal electrodes that similarly just obstructed micturition. We think it almost certain that no external device can stimulate all the motor fibres to the closing muscles with sufficiently little discomfort to allow long-term use in patients with intact sensation.

Summary

It is possible, through anal electrodes that we have designed specially for the purpose, to stimulate all the motor fibres of the pudendal nerves and thus cause maximal contractions of the muscles that they innervate. Anal and vaginal devices now in use for treating incontinence do not do this.

The force exerted by the anal sphincter under tetanic stimulation of its motor nerve fibres is, during the first few seconds, greater for high than for low frequencies of stimulation. But the sphincter fatigues more at high frequencies, so that if the force is measured between the 3rd and the 10th minute of stimulation it is greater for 12 pulses/sec than for 54 pulses/sec; 24 pulses/sec gives intermediate force. The fatigue is almost complete in 2 minutes.

The opening pressure for retrograde flow through the external sphincter of the urethra is roughly 120 mm Hg during prolonged maximal tetanic stimulation at 12 pulses/sec, and roughly 90 mm Hg during prolonged maximal stimulation at 54 pulses/sec.

Stimulation through our anal electrodes with shocks large enough to cause maximal contraction of the pelvic floor muscles causes in both sexes, at 12 or 24 pulses/sec, complete inability to expel urine during at least 10 minutes. We give evidence that the inability is due to the contraction of the striated muscles that close the urethra, not to inhibition of detrusor contraction. The stimuli do tend to inhibit detrusor contraction, but this tendency can be overcome with practice.

We confirm published observations that total bilateral pudendal block is compatible with continence and with voluntary micturition. Continence is sustained against 110 mm Hg lung pressure. Micturition, though possible, is slowed.

We wish to thank our volunteer subjects for their fortitude and efficient collaboration, and Mr J. R. Friend, MRCOG, for performing the pudendal block.

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A Double Blind Trial of a Polyene Macrolide—Nystatin—in the Treatment of Benign Prostatic Hyperplasia in Man

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Some patients presenting with the symptoms and signs of benign prostatic hyperplasia who require surgical treatment are poor operative risks on account of age or coincidental pathology. It is tempting to search for a drug rather than an operative form of treatment in these patients. Several drugs have been advocated in the past and recently some attention has been focused on the polyene macrolide group because they were reported to cause a reduction in volume of the hyperplastic prostate of aged dogs (Gordon and Schaffner, 1968). We therefore decided to investigate this in patients with benign prostatic hyperplasia. Nystatin was selected as the polyene macrolide of choice because it can be given by mouth and is known to be safe. A brief preliminary account of the trial when incomplete has already been made (Theodorides, Bourke and Griffin, 1972).

In any assessment of a medical treatment for the benign prostate the main question is whether it will prevent an operation. It is from this standpoint that the present trial will be assessed.

Patients and Method

The trial was of a double blind type using nystatin and a placebo. The placebo tablet which was of similar shape and colour to nystatin was made of an encompress of calcium phosphate and lactose. A trace of iron (0-10 parts per million) may be present in the encompress. Both nystatin and the placebo were similarly coated with methyl cellulose in chloroform/alcohol and riboflavin was the pigment used. Each tablet of nystatin contained 500,000 units of the drug.

Six weeks was chosen for the duration of the trial as this was the average time a patient would remain on the waiting list before admission to hospital for elective operative treatment of benign prostatic hyperplasia.

Patients were selected for entry to the trial when placed on the routine waiting list for operation. The indications for prostatectomy were those in general use (Blandy, 1971) and did not change during the period of the trial. Although flow measurements were not made the clinical criteria for the necessity for operation were those in common use, namely,

1. The estimate of the volume of residual urine as shown by the post-micturition bladder film in the excretion urogram.
2. The presence of detrusor thickening, trabeculation, sacculation and diverticula formation.
3. The patient's evaluation of his urinary frequency and his stream and
4. The development of acute retention of urine during or before the period of observation.

We deliberately did not attempt to evaluate the size of the gland by rectal examination since this is notoriously unreliable in the anaesthetised, let alone the unanaesthetised subject. Nor did we make use of planimetry of the prostatic shadow since in our hands this could not be correlated either with the mass of prostatic adenoma removed at operation or with the degree of outflow obstruction to the bladder. The patient was interviewed by one of us, the possible advantages of the trial were explained and his free consent obtained. An excretion urogram and liver function tests (bilirubin, alkaline phosphatase, zinc and thymol turbidities, serum glutamine oxalo-acetic transaminase) were estimated before commencing the trial. For the biochemical estimations a Technicon AutoAnalyzer was used.

Patients were then instructed to take 1 tablet at 8-hourly intervals every day for 6 weeks.

Clinical progress was assessed every 2 weeks and at the 6th week a decision was made whether operation was still indicated or not. At this time the investigations noted above were repeated. If operation was now considered unnecessary, the patient was removed from the waiting list but seen at 3-monthly intervals. Otherwise the operation was performed within a few days.

Any patient could be withdrawn from the trial if this seemed to be clinically indicated. At no time during the trial did the clinicians know which substance any of the patients was taking.

Results

39 patients were admitted to the trial. One patient receiving nystatin developed a skin rash which subsided on stopping the drug. He was withdrawn from the trial. Another patient was withdrawn because of a cardiac infarct. A third patient defaulted, but subsequently needed prostatectomy.

Table I

Result of Nystatin and Placebo in Patients with Benign Prostatic Hyperplasia

	Nystatin	Placebo
Operation during or after trial	14	14
Carcinoma found at operation	2	1
Not operated on within 9 months of completion of trial	4	4*
Withdrawn from trial or defaulted	1	2

* One of these patients needed operation at 18 months.

14 patients in both the nystatin and placebo groups required operative treatment. Four patients in both groups have not required surgery within 9 months of completing the trial (see Table I).

Three patients were found to have carcinoma at operation.

The excretion urograms were unchanged in either group. The liver function tests showed no abnormalities in either group of patients except in one who was mildly jaundiced at entry to the trial and was so at its conclusion. The degree of jaundice did not appear to be altered by nystatin.

Discussion

The results of the present study show that nystatin given in the dose used here for a 6-week period did not reduce the number of patients who required operative treatment for benign prostatic hyperplasia. A higher dose might have been more effective. This may be useful to know when considering which dose to use of the other polyene macrolides which are at present being investigated in prostatic hyperplasia (Scrip, 1972). The duration of therapy may have been too short. Six weeks was selected for the duration of the trial since this was the time a patient usually had to wait for his operation. In any case it is doubtful if such trials should be continued for much longer since 3 of our patients turned out to have cancer and not benign hyperplasia—an experience noted by others (Franks, 1972; Gow, 1972). It is said of the polyene macrolide, candicidin, that although it may be successful in some cases it is not suitable for the treatment of acute retention because "it takes time to work" (Scrip, 1972). In view of the well documented risk of undetected neoplasia in these patients (Franks, 1972; Gow, 1972) and confirmed in our series, any drug which is to be useful in benign prostatic enlargement should have a short latent period.

The trial of medrogestone (Rangno *et al.*, 1971) an oral progestogen and antiandrogen was criticised (*British Medical Journal*, 1971) because it lacked evidence of shrinkage of the prostate by the 2 accepted criteria of objective assessment—urine flow rate and residual urine estimation (Castro, Griffiths and Edwards, 1971; *British Medical Journal*, 1971; Castro, 1972; Castro and Griffiths, 1972) and only claimed subjective improvement. Aubrey and Khosla (1971) recently used SH582 and a placebo in a double blind cross-over trial and found that the mean volume of residual urine was "significantly reduced" from 76·5 to 42·2 ml. In surgical terms, however, this reduction is meaningless (*British Medical Journal*, 1971).

The present study may be criticised on the grounds that its evaluation is clinical and not objective. But in practice the indications for prostatectomy are so complex and interrelated that they do not lend themselves to any simple and objective method of measurement. On the one hand, whilst symptoms are notoriously untrustworthy and difficult to evaluate (Castro, Griffiths and Shackman, 1969; Castro and Griffiths, 1972) they may signify impending obstruction, or demand surgery for their relief and even if they defy quantitation they still have to be reckoned with. On the other hand, none of the available "objective" methods withstand criticism; the voiding flow-rate may vary with different bladder volumes in the same subject (Castro and Griffiths, 1972; Garrelts, 1972) and in any case it takes no account of the compensatory hypertrophy of the detrusor (Garrelts, 1972) which itself may be dangerous from the development of sacculations and diverticula. To take detrusor hypertrophy into account one must introduce catheters either through the urethra (Castro and Griffiths, 1972; Garrelts, 1972) or through a suprapubic incision —neither method without discomfort or the slight risk of infection (Garrelts, 1972). Attempts have been made to calculate the outflow resistance at the neck of the bladder from the detrusor pressure and the rate of flow of urine during voiding, arriving at conclusions through the ingenious application of concepts torn from their hydrodynamic context (Rankin, 1967; Castro, Griffiths and Edwards, 1971; Castro and Griffiths, 1972; Garrelts, 1972). Again, many attempts have been made to assess the volume of the prostate by objective means, usually by careful planimetry of the shadow thought to represent the prostate in the post-voiding radiograph of the excretion urographic series (Griffiths and Castro, 1970; Castro *et al.*, 1971; Castro and Griffiths, 1972). Here the drawback is that outflow obstruction in the elderly man is seldom related to the size of the prostate: it is indeed a urological commonplace that the worst outflow obstructions occur with the smallest fibrous glands (Franks, 1970; *British Medical Journal*, 1971). Nor is it logical to assume that what shrinks the gland will do it good: one can imagine a bulky soft adenoma being turned into a tight little fibrous ring with deterioration of the outflow resistance.

It was for these reasons that we deliberately chose to keep to clinical considerations, and tried to answer the real question posed by any new pill for the prostate—"will it spare the old man an operation?" Evidently the answer given here must be "no—in the circumstances of this trial". Clearly if more nystatin had been given for longer, it might have done more good.

The study has not however been without value: it shows once again the need for controls in evaluating any new treatment for the prostate (Castro *et al.*, 1971; Castro and Griffiths, 1972): it reveals the "placebo" effect, so clearly shown by Castro and his associates (Castro *et al.*, 1971; Castro and Griffiths, 1972) and before them by Clarke (1937). Evidently there is good reason for caution in deciding on a prostatectomy, and possibly even some virtue in a waiting list which imposes a delay between the decision to operate and the operation itself. Whether the 8 men who seemed to improve after 6 weeks of the nystatin or the placebo will later need prostatectomy for retention or subsequent relapse of their symptoms can only be shown by a longer term trial: one of them subsequently came to operation: the others are being followed. Prostatism is a disorder characterised by its ups and downs. Since delay carries with it the risk of acute retention and development of infection, and since both these complications increase the risk of prostatectomy several fold, it may be unwise to accept with too much complacency an apparent clinical improvement whether judged by symptoms or backed up by the evidence of the excretion urogram.

Summary

Gordon and Schaffner (1968) showed that anti-fungal drugs of the polyene macrolide group caused a reduction in volume of the hyperplastic prostate of aged dogs. It was, therefore, decided to investigate the effect of nystatin in patients with benign prostatic hyperplasia. In a double blind trial of 6 weeks' duration nystatin in doses of 500,000 units 8-hourly when taken orally was without effect when compared with a placebo.

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Liposarcoma of Paratesticular Origin: A Case Report

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Malignant connective tissue tumours of paratesticular origin are rare and are hardly ever considered in the differential diagnosis of intrascrotal swellings. Because of their rarity and the possibility that they have a better prognosis than the commoner testicular neoplasms, we think that a report of a liposarcoma of paratesticular origin is worth recording.

Clinical Findings

A. W., a 68-year-old male was referred to the surgical out-patient clinic with a 1-month history of a painless swelling in the left groin. Systematic enquiry at that time failed to elicit any other complaint but on subsequent questioning he admitted to a dragging sensation and swelling in the right side of the scrotum which had been present for the preceding 2 months.

On examination there was a left indirect inguinal hernia, the right inguinal canal was intact. On the right side there was an intrascrotal swelling which was continuous with the spermatic cord; the right testis could not be separately palpated. The swelling was of a rubbery consistency, it was not tender and did not transilluminate. The left testis, epididymis and spermatic cord were normal; the prostate was hypertrophied (Grade II). No other abnormal physical signs were detected.

The clinical diagnosis was that of a left indirect inguinal hernia and a right testicular neoplasm. The patient was admitted for surgical treatment. The left inguinal hernia was confirmed at operation and a Bassini repair performed. Exploration of the right side of the scrotum showed that the testis was normal and that there was a tumour which appeared to be arising from the spermatic cord in the region of the epididymis, the latter being unidentifiable. A formal right orchidectomy with ligation and division of the spermatic cord at the internal inguinal ring was performed, followed by a Bassini herniorraphy. The left side of the scrotum was not explored.

The postoperative course was uneventful; the patient was referred for the opinion of a radiotherapist who thought that a course of radiotherapy was worthwhile. Eight months after the operation the patient is well, with no clinical evidence of recurrence.

Pathology

Naked Eye

The specimen consisted of an enlarged smooth mass weighing 210 g. Cut surfaces showed that lightly attached to a macroscopically normal testis there was a well demarcated tumour, 10·0 × 10·0 × 5·0 cm. The tumour was predominantly light yellow in colour and showed small areas of necrosis, haemorrhage, cyst formation and fibrosis. The epididymis could not be identified; the 6·0 cm of attached spermatic cord appeared normal.

Histology

Sections show a well demarcated cellular malignant tumour of connective tissue origin (sarcoma). The tumour consists predominantly of sheets of closely packed spheroidal cells with either a finely granular or vacuolated cytoplasm (Figs. 1 and 2); there is some nuclear pleomorphism but mitotic figures are scanty. There is an abundance of sudanophilic material (Fig. 3) in the tumour cells and this fat is unrelated to the small and numerous areas of cystic degeneration and haemorrhage. Mixed with this spheroidal cell pattern are areas of slightly pleomorphic spindle cell tumour (Fig. 4). There is no malignant infiltration into the normal testis, neither can tumour be seen in sections examined from the whole length of the excised spermatic cord.

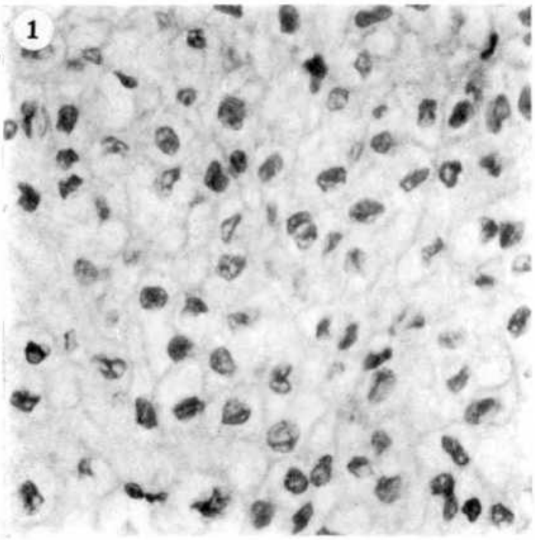

Fig. 1. Liposarcoma showing spheroidal cell pattern. H & E. × 500.

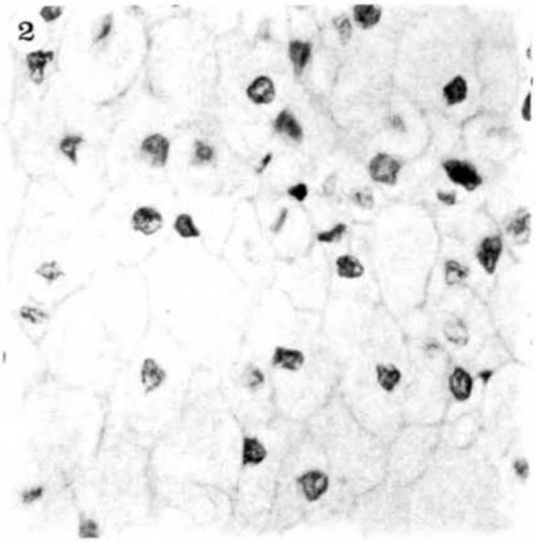

Fig. 2. Liposarcoma showing clear vacuolated cells. H & E. × 800.

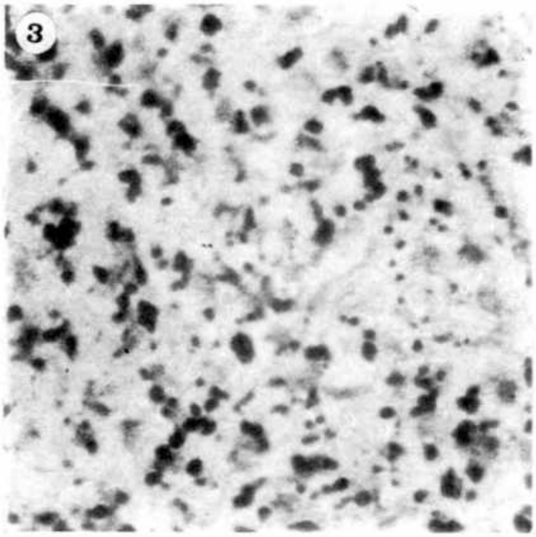

Fig. 3. Sudanophilic material in tumour cells. Oil Red "O". × 500.

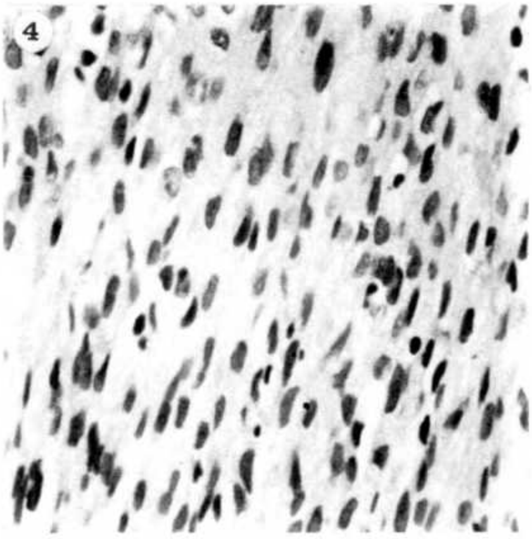

Fig. 4. Liposarcoma showing spindle cell pattern. H & E. × 500.

Discussion

Liposarcoma of paratesticular origin is rare. In the 6 years 1958-63, the Testicular Tumour Panel examined 1,050 neoplasms of the testes and appendages (Collins and Pugh, 1964). The majority (995) were testicular tumours; there were 27 examples of non-epithelial paratesticular tumours of muscular or connective tissue origin. Only 2 of these were accepted as liposarcoma. Dreyfuss and Goodsitt (1960) reported a liposarcoma of the spermatic cord and Lundblad, Mellinger and Gleason (1967), in a review of malignant tumours of the cord found 1 case. Datta, Singh and Bapna (1971) found 8 cases reported in the literature, to which they added 1. This review included the case reported by Dreyfuss and Goodsitt (1960), but did not include the 2 seen by the Testicular Tumour Panel (Collins and Pugh, 1964).

Although 90% of paratesticular tumours within the scrotum are believed to arise from the spermatic cord (Prince, 1942), the size of the present tumour makes it difficult to be certain as to the precise site of origin. Epididymis and spermatic cord are possible sites. The epididymis in the present case could not be identified, and although the epididymis does not normally contain fat, occasionally a little may be found in the covering. Although no tumour was seen in sections examined from the whole length of the excised cord, origin within its intrascrotal part cannot be completely excluded.

The histology of the tumour is that of a malignant mesenchymal tumour, predominantly consisting of slightly pleomorphic spheroidal cells containing sudanophilic material and with some spindle cell areas. These features are similar to other cases reported where histological details have been given (Dreyfuss and Goodsitt, 1960; Collins and Pugh, 1964) and are no different from liposarcoma at other sites in the body. A spindle cell pattern is a well recognised component of liposarcoma (Mackenzie, 1970).

Insufficient examples of paratesticular liposarcoma have been reported to draw valid conclusions as to prognosis, but it does appear that like other malignant tumours of paratesticular origin there is a considerable variation in behaviour (Thompson, 1936; Fitzpatrick *et al.*, 1952).

Our patient is alive and well 8 months after orchidectomy. Of the 2 patients recorded by the Testicular Tumour Panel (Collins and Pugh, 1964), 1 aged 29 years was alive and well 10 years following removal of the tumour. The other patient, 42 years old, rapidly developed a local recurrence. The patient with liposarcoma of the cord reported by Datta, Singh and Bapna (1971) was alive and well 5 years after orchidectomy; of the 8 cases previously reported and reviewed 5 were well. Two died, 1 of myeloid leukaemia shortly after the liposarcoma had been diagnosed; the other patient had a slowly growing intrascrotal swelling for 12 years prior to diagnosis; growth had been rapid for 3 years before the diagnosis was made. All these patients were treated by orchidectomy, only the case reported by Garcia and his colleagues (1968) and included in the review of Datta, Singh and Bapna (1971) had received postoperative radiotherapy for widespread metastases.

The clinical diagnosis of paratesticular tumours is difficult and the differential diagnosis includes almost all intrascrotal swellings, even if a testis cannot be separately distinguished from the tumour as was the case in our patient. Certainly paratesticular tumours should be considered in any intrascrotal swelling which is thought to be discrete from the testis, regardless of the rate of growth, the presence or absence of pain and whether or not it transilluminates (Satter, Heidner and Wear, 1959). Benign tumours require only local excision; malignant tumours require orchidectomy with high ligation and excision of the spermatic cord. Banowsky and Schultz (1970) reviewed the literature on malignant tumours of the spermatic cord and tunica. They concluded that, contrary to current opinion, the majority of these tumours metastasised by the lymphatic system and not by the blood stream, and therefore retroperitoneal lymph node dissection should be considered more frequently. Although only 12 cases of liposarcoma have now been reported it appears that they are in general less malignant than testicular tumours and that orchidectomy with high ligation and excision of the spermatic cord is probably the treatment of choice.

Summary

A liposarcoma of paratesticular origin is reported; this is the 12th recorded case. A survey of previously published cases suggests that there is a considerable variation in behaviour, but that

they are probably less malignant than the commoner testicular neoplasms, and that orchidectomy with high ligation and excision of the spermatic cord is adequate.

We thank Mr Adrian Litton for permission to publish and Mr G. F. Headen, FILMT for the photomicrographs.

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Short Case Reports

Lightbulb Calculus in the Ureter

Foreign bodies that are located in the ureter are a rare entity. In their reviews, Osmond (1953) and Bretland and Blacklock (1968) found only 7 cases of foreign bodies of the ureter that were possibly due to retrograde migration. This case reports the formation of a foreign body concrement upon a cystoscopic lightbulb.

Case Report

A 62-year-old paraplegic with bilateral vesico-ureteral reflux underwent cystolitholopaxy for eggshell calculi in the bladder using a Lowsley's biopsy forceps. Six months later he developed right flank pain and fever. An intravenous pyelogram showed delayed function with an opacity on the right at L4 (Fig. 1). A retrograde ureterogram confirmed it was in the ureter. Ureterolithotomy was performed. The stone had a cystoscopic lightbulb in the centre (Fig. 2).

We have been successful in using the Lowsley biopsy forceps for soft eggshell calculi of the bladder forming secondary to a Foley catheter. Unfortunately, breaking lightbulbs has been a frequent problem. In the present case, this was further complicated by the presence of vesico-ureteral reflux.

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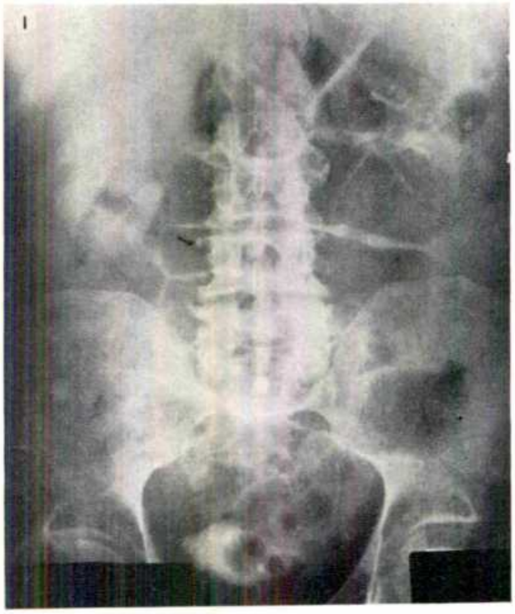

Fig. 1

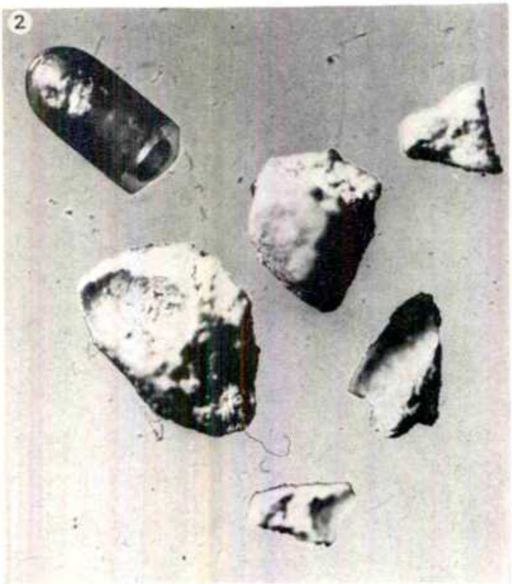

Fig. 2

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British Journal of Urology (1974), **46**, 472

Adrenal Metastases from Renal Carcinoma Diagnosed by Selective Renal Angiography

Although adrenal metastases from renal carcinomas are not uncommonly found at autopsy (6 out of 26 autopsies of renal tumours in Oxford, 1959-70) these are rarely diagnosed during life.

Case Report

A man aged 49 had intermittent haematuria for 18 months. An I.V.P. demonstrated a large mass in the upper pole of the left kidney with the upper calyces filling retrogradely from the renal pelvis. Renal angiography confirmed a large vascular mass, but in addition showed 2 areas of tumour type circulation in the left adrenal area.

The kidney and adrenal were removed. A large adenocarcinoma occupied the upper part of the kidney and 2 nodules of tumour were present in the adrenal. A large subphrenic venous plexus communicated with the tumour and adrenal but was not invaded either macroscopically or microscopically.

As an adrenal branch of the renal artery is often demonstrated at renal angiography, it seems surprising that adrenal metastases are not more frequently demonstrated. Serial changers do not always produce the clearest radiographs, but a simple angiographic Bucky technique may give better detail (Wright, 1973). Statistics have shown that ipsilateral adrenal deposits are more common than contralateral. Other demonstrations of such deposits have been made by Kahn, Wise and Robbins (1968) and by Lang (1971).

My thanks are due to Mr R. C. Baillie, for referring this case for angiography.

F. W. Wright,
Churchill Hospital, Oxford

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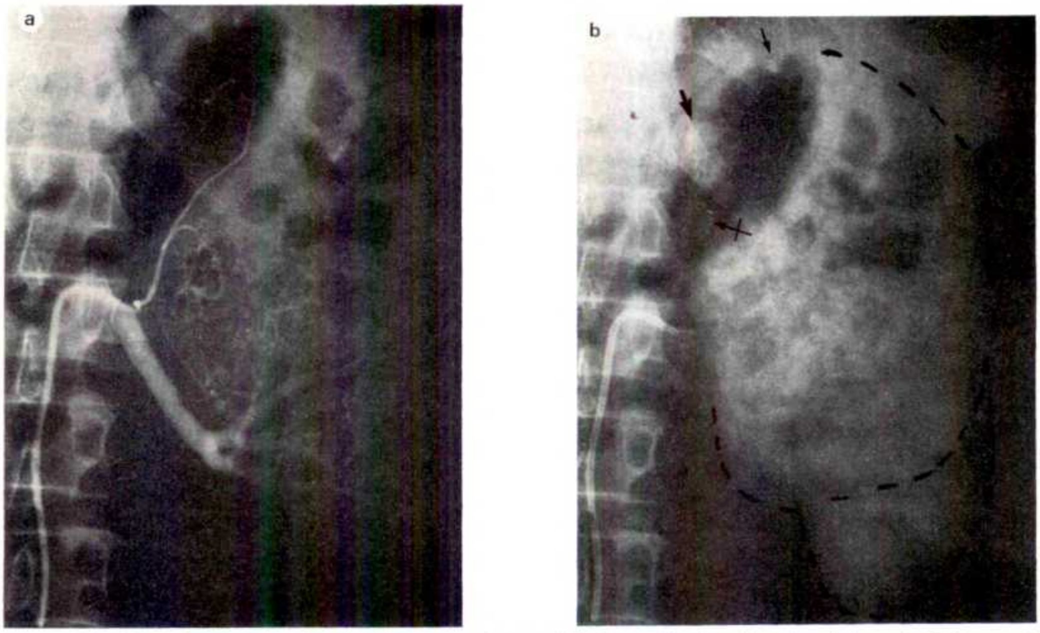

Fig. 1. Selective left renal arteriogram. (*a*) 1 second—arterial phase: showing the adrenal branch of the renal artery and a large vascular tumour occupying the upper $\frac{2}{3}$ of the kidney. (*b*) 5 seconds—nephrogram and venous phase: showing the tumour and the 2 adrenal metastases, one minute (thin arrow), but the other about 1·5 cm in diameter (thick arrow). The faintly opacified lower pole of the adrenal was also visualised (crossed arrow).

CONFERENCES AND COURSES

Royal Postgraduate Medical School, Hammersmith Hospital

Recent Advances in Urology

(28th October to 1st November 1974)

Applications are invited from Consultants, Senior Registrars and University Teaching and Research Staff for the above course.

Topics to be covered will include: Pharmacology, Immunology, Surgical techniques, Hormone therapy and Cytotoxic therapy.

Fee: £25 (excluding catering charges).

This course is approved for support under the Advance Postgraduate Training Scheme for National Health Staff.

Further details and application forms from the School Secretary, Royal Postgraduate Medical School, Hammersmith Hospital, London, W12 0HS.

Congrès Français d'Urologie

French Congress of Urology

The 68th French Congress of Urology will be held in Paris from 22nd–25th September, 1974.

The main subject of the conference will be "Neurogenic Bladders". Details may be obtained from the General Secretary: Professor D. Grasset, Clinique Urologique, Hôpital Saint-Charles, C.H.U.—34000 Montpellier, Paris.

Book Reviews

Urinary Calculi. Recent Advances in Aetiology, Stone Structure and Treatment. Edited by L. Cifuentes Delatte, A. Rapado and A. Hodgkinson. Pp. x+364 with 165 illustration. Basel: S. Karger, 1973. £18·85.

This is the proceedings of an international conference held in Madrid in September 1972. It contains 54 papers but no report of the discussions or of the final session devoted to future research in the field. As the title suggests, the papers cover many aspects of urolithiasis in the western world.

The aetiology of urinary stone disease remains to a great extent an enigma. There are papers dealing with the metabolic basis of stone formation. Other investigators have measured excretion, concentration and saturation in urines from normals and stone-formers, and studied the effect of diet on the composition of urine. Different results are reported, but it is generally agreed that factors other than these are involved in the formation of the mineral matter of stones. Inhibitors of nucleation, crystal growth and aggregation are currently hailed as being of importance, and work on their properties, isolation and detection are reported and to a certain extent reviewed.

Of interest is the section on therapy. Most forms of urolithiasis can now be treated, and several authors have presented their experiences and findings on the use of the different drugs available, and on stone recurrence rate and urinary saturation during treatment.

The section on stone analysis deals mainly with well-established techniques such as optical crystallography and infra-red spectroscopy, but other methods like thermal analysis and neutron activation analysis are presented. The electron microscope is of limited use in studying overall stone composition, but it has revealed fascinating details of the ultrastructure of calculi. However, preparation of specimens for the scanning electron microscope can introduce artefacts, and some pictures of matrix in intact stones should be interpreted with caution until verified by other workers.

At most conferences, papers vary considerably in scientific quality, but the great majority of these are of a high standard. The layout of the book is very pleasing and only the price is likely to preclude individuals interested in the field from buying a personal copy.

D. J. S.

Indanyl Carbenicillin. International Congress Series No. 314. Editors, H. Swartz and F. E. Storari. Amsterdam: Excerpta Medica. 1973. US $12·40.

This book presents the Proceedings of a Symposium held at the Royal Society of Medicine, London, 12th April 1973 on Indanyl Carbenicillin (Carindacillin). This is the 5-indanyl ester of carbenicillin which unlike its parent compound is well absorbed from the gastro-intestinal tract, after which it is rapidly hydrolysed into the active component carbenicillin, and indanol. At the above symposium papers were presented describing the blood and urine levels obtained in normal adults and in those with varying degrees of renal impairment. Also described were the results of treatment of urinary infections due to a variety of bacteria in patients with normal urinary tracts and in those with underlying pathological conditions of the urinary system.

From the papers presented at this symposium indanyl carbenicillin would appear to be indicated in the treatment of urinary tract infections due to sensitive *Pseudomonas*, and other bacteria which are resistant to existing anti-bacterial agents which can be administered orally in ambulant inpatients or outpatients. Adequate blood levels are not achieved for the treatment of systemic infections due to these types of organisms and in severe renal failure sub-therapeutic levels are present in the urine. As might be expected the results obtained in the treatment of patients with underlying disease of the urinary tract were not as satisfactory as those achieved in patients with normal urinary tracts. Side-effects were not frequently encountered and were mainly gastro-intestinal, being nausea, vomiting, diarrhoea and flatulence.

H. R. I.

The Urological Management of the Patient Following Spinal Cord Injury. By John W. Pearman and Ernest J. England. 1st Edition. Pp. xviii+280 with 76 illustrations. Springfield, Illinois: Charles C Thomas. 1973. $15·50.

This handsome volume is a highly successful blend of scientific primer and practical manual, which offers the reader information not only in a highly specialised urological field, but also about the modern concept of total care in a paraplegic centre. That one of the authors is a microbiologist suggests correctly that the emphasis in their unit is on the prevention and early treatment of urinary tract infection which has always been the main cause of death in chronic paraplegia. In their hands, intermittent catheterisation combined with instillation of an antibacterial solution into the bladder, has resulted in significant bacteriuria in only 0·5% of catheterisations with half of the patients remaining sterile for over 2 months, and 90% of them discharged catheter-free with sterile urine. These outstanding results have been contributed too by dip-slide culture of every specimen of urine which has facilitated prompt diagnosis and treatment of infection. Although the number of patients involved in the improved regime is small, the indications are that they may have experienced earlier return of reflex bladder activity and a lower incidence of surgical intervention.

The few criticisms which come to mind are surgical and related to policy rather than technique. For example, the proposition that anaesthetic block of the bladder mucosa or pudendal nerves has any long-term value, is doubtful in theory and unproven in practice. Again external sphincterotomy is replacing bladder-neck resection as the primary procedure for inefficient reflex bladder-emptying, but no doubt the next edition will reflect this change of view. In this connection "stricture" is an inaccurate term for most of the non-spastic obstructions in the membranous urethra. Overstretching of the urethra is not mentioned as a useful means of reducing residual urine in the female.

Finally, it is time that arguments about arbitrary amounts or percentages of residual urine were laid to rest—surely an acceptable residual urine is one associated with continued sterility of the specimen and radiological normality of the upper urinary tracts.

N. O. K. G.

Renal Disease. Edited by SIR DOUGLAS BLACK. 3rd edition. Pp. 871 with 397 illustrations. Oxford: Blackwell Scientific Publications. 1972. £13.

When this book first appeared in 1962, the editor was careful to point out that it was not intended to be comprehensive, but such was his choice of topics and authors that it did in fact contain an advanced and reasonably full account of the more important elements of nephrology. It says much for Sir Douglas Black's skill that, in compiling each successive edition, he has contrived to make substantial changes in both the contents and the authorship of the work without allowing it to degenerate into a formless collection of learned papers; indeed, some readers may well consider that the latest edition provides a more balanced and up-to-date account of nephrology than did either of its predecessors.

Most of the new or revised material reflects the advances and changes in emphasis which have occurred since the second edition was published. Thus the opening chapter on renal anatomy now contains illustrations and descriptions of the ultrastructure of the kidney, the new chapter on electron microscopy centres on the value of this technique in the study of glomerular disease, and the detailed description of the mechanisms of urinary concentration and hydrogen ion excretion which appeared in the previous edition have been replaced by erudite new chapters on the control of sodium reabsorption, the glomerular basement membrane and micropuncture.

In addition, many of the chapters dealing with clinical topics, including those devoted to glomerulonephritis, urinary tract infections and pyelonephritis, acute renal failure, urinary lithiasis and renal disease in childhood, have been entrusted to new authors. By employing this device the editor has not only ensured that these chapters have undergone radical revision but also that a large part of the text will have a fresh appeal to readers who are familiar with previous editions.

Excellent though it is, the book is not entirely above criticism. Some of the chapters are surely too verbose and the text suffers from the variations in academic pitch and literary style which are almost inevitable in a multi-author textbook. It is also surprising that space has not been found for a systematic account of renography and other isotopic methods of investigation, although it is true that brief references to this topic are to be found in the rather elementary new chapter on urinalysis and assessment of renal function.

All in all, however, the latest volume maintains, even exceeds, the high standards set by its predecessors.

A. R. H.

ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

La Nouvelle Presse Médicale

By John Grieve

"Arteriographic Signs in Primary Hyperparathyroidism." J. C. Gaux, V. Bismuth, D. Fritel, J. M. Brisset, M. Blery, A. Baglin and J. P. Fendler. (1973, **2**, 2733-2737.)—In 10 patients in whom arteriography of the parathyroid has been done direct signs have been found in 6 patients. The signs were increased vascularity and opacification of the gland and in the 6 cases showing these changes operation and location of the adenoma were made easier. In the other 4 there was hypertrophy of the inferior thyroid artery and opening of its second loop. Although these signs were less clear the 4 remaining cases all had adenomata and these were successfully treated.

Annals of Surgery

By Peter Edmund

"Significance and Treatment of Occult Obstructive Uropathy Complicating Crohn's Disease." G. E. Block, W. E. Enker and J. B. Kirsner. (1973, **178**, 322-332.)—The authors report their experience with 27 patients exhibiting Crohn's disease and right ureteral obstruction treated from 1967 to 1972. During the same period 106 patients suffering from Crohn's disease primarily involving the terminal ileum and ascending colon had resections but the incidence of ureteral obstruction is exaggerated since the majority of patients were referred from elsewhere. The discussion following the paper is helpful to achieve a true perspective of the disease. The average age at operation was 25·5 years and the average duration of known granulomatous disease was 3·9 years. Two patients presented with primary urinary symptoms. The most useful preoperative diagnostic examination was the excretion urogram and the authors draw special attention to the value of pre-voiding views of the bladder where, in patients with severe ileal disease, the right posterior dome of the bladder was persistently indented. This deformity corresponded to the outline of the inflamed and thickened small bowel and returned to normal after resection of the involved bowel. At operation 24 (89%) patients had a fistula or sinus tract to the retroperitoneum and 11 (41%) patients had frank abscesses of the anterior retroperitoneal compartment. In all cases the right ureter was encased in a cicatrix of retroperitoneal fibrosis and it was considered that the obstructive uropathy indicates the presence of the classical complications of Crohn's disease, sinus, fistula or abscess. Obstructive uropathy was an indication for appropriate small bowel surgery and for ureterolysis with resection of the anterior portion of the fibrotic sheath. Follow-up uropathy revealed complete resolution of the obstructive uropathy.

The authors advocate three principles of management, the recognition of an anterior retroperitoneal space infection, resection of the segment of small bowel initiating the complication and the relief of the mechanical obstructive uropathy.

"Renal Transplantation for Diabetic Glomerulosclerosis." J. S. Najarian, C. M. Kljellstrand, R. L. Simmons, T. J. Buselmeir, B. von Hartitzsch and C. Gotez. (**178**, 477-483.)—Uraemia causes a significant number of deaths in patients with juvenile diabetes. As dialysis is associated with a high morbidity and low rate of survival the authors report that patients with diabetes have been routinely accepted for renal transplantation at the University of Minnesota from 1966. 40 patients, all with severe hypertension, received 45 transplants between 1969 and 1972. All but 1 case had bilateral nephrectomy. 31 patients were alive at 4 months to 4 years after transplantation. The 2 major complications were myocardial infarction and urinary leakage. Although the diabetic patient with renal failure has a higher risk of death and of severe complications than has the non-diabetic patient it is concluded that the results of transplantation are markedly better than those reported for chronic haemodialysis. Biopsies taken up to 3 years after transplantation have not shown any recurrence of Kimmelstiel-Wilson changes although the authors warn that a longer period of observation will be necessary. Eyesight changes were found to stabilise following renal transplantation and both neuropathy and bladder dysfunction usually improved.

"Changing Patterns in Surgical Infection." W. A. Altemeier, R. P. Hammel, E. O. Hill and S. Lewis. (**178**, 436-445.)—This report summarises the microbial aetiology of surgical infections from the Department of Surgery at the University of Cincinnati Medical Centre during the past 28 years. Since 1956 there has been an increasing incidence of Gram-negative infections whilst the effects of treatment have been seen in that 80% of serious infections developed while the patients were on antibiotic prophylaxis or therapy. An increasing number of infections with "L" forms and other atypical bacterial forms have been noted in association with antibiotic therapy and with recurrent thrombo-phlebitis and thrombo-embolic disease. A cyclical variation in staphylococcal resistance to penicillin has also been demonstrated.

The work indicates the need for constant surveillance by hospitals and Dr Altemeier forecasts an increase in the number of staphylococcal infections in the next 5 years. This overall increase is likely to be associated with an increase in the antibiotic resistance of these staphylococcal infections.

"Factors Responsible for Urinary Fistula in the Renal Transplant Recipient." G. M. Hricko, A. G. Birtch, A. H. Bennett and R. E. Wilson. (**178**, 609-615.)—Urinary fistula after renal transplantation is a severe and often lethal complication. The 20-year experience of renal transplantation at the Peter Bent Brigham Hospital is reviewed by the authors to examine the factors which may predispose to this complication. The overall incidence for fistula formation in 238 patients was 22·7% but the incidence over the last 120 patients (since 1970) has been reduced to 6·7%.

The relationship of presence of multiple renal arteries to urinary fistula formation is highly significant and kidneys from living donors with multiple renal arteries had the highest incidence of fistula, regardless of the type of urinary anastomosis used. This did not apply to multiple renal arteries in the cadaver donor kidneys where there was no greater incidence than with kidneys with single renal arteries from living or cadaveric kidneys. The authors suggest that the presence of multiple renal arteries may make the pelvic and ureteral blood supply more tenuous and that the greatest care is necessary to preserve this blood supply.

"Current Status of Bilateral Adrenalectomy for Advanced Prostatic Carcinoma." J. BHANALPH, M. J. VARKARAKIS and G. P. MURPHY. (1974, **179**, 17-23.)—The authors report their results of bilateral adrenalectomy in 26 patients with proven disseminated prostatic carcinoma and compare their survival with patients at the same stage of disease with clinical remission after orchidectomy and oestrogen therapy. In this series the patients with a long period of subjective response had a long survival, whilst bilateral adrenalectomy in patients who had relapsed after previous hormonal ablation had a shorter survival time and a shorter period of subjective improvement than those who had not relapsed.

Bilateral adrenalectomy should benefit only patients with androgen dependent disease but the problem remains to identify these patients to determine whether increased survival and any objective response can be satisfactorily correlated. The one year survival of patients after adrenalectomy (pituitary intact) was 53% where as only 25% of patients who had relapsed after castration and hypophysectomy had a one year survival.

Clinical improvement correlated with the reduction in serum acid phosphatase levels after adrenalectomy but no consistent change of total urinary 17-ketosteroids or plasma testosterone were seen.

For assessment the authors chose a starting point at 4 years after initial diagnosis, but this may be questioned in a disease where the natural history is so variable. The paper illustrates the difficulty in assessing any form of palliative treatment but the authors conclude that further improved results following adrenalectomy for relapsed advanced prostatic carcinoma may be anticipated.

Annales Chirurgiae et Gynaecologiae Fenniae

By J. V. MANDEL

"Renal Injuries." M. SAARIALHO. (1973, **62**, 278-285.)—Based on a series of 59 renal injuries, the author tries to find out whether the fairly conservative treatment is the best possible. 54 injuries were caused by blunt trauma, and five were the result of shooting or knifing. 35 were mild contusions, 15 minor ruptures, and 5 patients were operated on immediately. The 4th group comprised severe complications; all of them required surgical intervention. Early nephrectomy was performed in 4 patients, heminephrectomy in 2, and suturing alone in 2. Late nephrectomy was done in two-thirds of the patients. The average stay in hospital was 14 days.

46 patients answered the follow-up questionnaire, 28 of them were asked to attend the Out-Patients Clinic. Of the 11 patients with grade two lesions who were treated conservatively, 5 had abnormal X-ray findings, none of them had hypertension. Two of the conservatively treated patients with normal X-ray findings had a raised blood pressure. It could not be proved in any of these patients that the hypertension was a sequel of the renal injury. The author is satisfied with the results of his conservative methods.

"Carcinoma of the Renal Pelvis and its Relationship to Analgesic Abuse." H. JUUSELA. (1973, **62**, 386-390.)—A clinical series of 17 patients suffering from carcinoma of the kidney pelvis, is presented. There were 11 males and 6 females. Haematuria was the most common presenting symptom. Intravenous urography and exfoliative cytology were most helpful with diagnosis. In 11 patients nephro-ureterectomy was done, in 3 radical nephrectomy, and in 2 resection of the renal pelvis. Two of the patients had deep X-ray treatment, postoperatively. The patients were followed up between 1 and 5 years after operation. Six died during this period, 7 are alive and well, 2 have papillomata in the bladder, and another 2 are suspected to suffer from a pelvic tumour in the other kidney.

In this group, 3 patients who indulged in taking analgesics containing phenacetin, and 2 possibles were found. The aetiology of carcinoma of the kidney pelvis is discussed.

Archivio Italiano di Urologia e Nefrologia

By JOSEPH MAGRI

"Indications and Limitations of Total Cystectomy." E. SIGNORELLI, B. FRAENZA and M. BELLONI. (1973, **45**, 11.)—A series of 46 cystectomies performed on one unit in a 10-year period up to 1972, was collected, 43 being for primary bladder tumour. Almost all patients were male. Complications included urinary fistula in 2 patients which healed spontaneously, and intestinal obstruction in 4, all of whom were re-operated; 1 died. Tumours were classified as Stage 2 in 21%, Stage 3 in 42% and Stage 4 in 37%. Types of urinary diversion were Coffey in 22, Mauclair in 20, Gersuny in 1, ileal conduit in 2 and cystoplasty in 1. Altogether 25 patients have died to date, 15 from metastases and 6 from renal insufficiency. Over the whole series survival at 3 years was 24%, at 4 years 17% and over 7 years 6%. This paper, which formed the main contribution towards a meeting of Lombardy urologists, incorporated an extensive exposition on the various investigations that can be applied to the diagnosis, staging and grading of bladder tumours, on the indications and limitations of the operation and on points in operative technique relating to the cystectomy itself and to the accompanying urinary diversion, and together with the contributions to the discussion took up the whole issue of the journal. A more detailed summary is beyond the scope of this brief.

"Bilateral Renal Angiomyolipoma not Associated with Tuberous Sclerosis; A Case Report." A. CARESANO, C. DEL FAVERO, R. PASSERA, A. V. BONO, G. GOMERI and L. BARATELLI. (1973, **45**, 131.)—Excretory pyelography in a 35-year-old woman presenting with severe haematuria demonstrated a normal right kidney and a distorted left pelvi-calyceal system with an irregular cortical outline. Selective renal angiography carried out bilaterally revealed appearances suggestive of angiomyolipoma (hamartoma). Left nephrectomy was rendered necessary by the profuse bleeding thus providing histological confirmation of the presumed diagnosis.

"Pedunculated Myxoma of the Ureter." F. Apicella and G. Tonazzi. (1973, **45**, 123.)—A case report of a benign ureteric tumour which was diagnosed radiologically in a 27-year-old woman presenting with renal colic and haematuria. Simple excision of the tumour was carried out which had a fusiform outline and measured 16 by 1·2 cm. Histological examination revealed its myxomatous nature similar to tumours described in the bladder, more usually in children.

"The use of Ketamine in Urological Endoscopy." R. Ravagnan. (1973, **45**, 93.)—Ketamine (chlorhydrate of 2-(O-chlorphenyl)-2-(methylamino)-cycloesanone) was administered intravenously as the sole anaesthetic agent in 500 patients undergoing a number of endoscopic procedures. The dosage used in 3 comparable groups was 1, 2 and 3 mg/kg. Side effects were many at all dose levels and included respiratory obstruction, tachycardia, arterial hypertension, hallucinatory episodes and delayed recovery. The frequency of these complications discourages the use of Ketamine, particularly in old patients and those with cardiovascular problems.

Deutsche Medizinische Wochenschrift

By John Grieve

"Reversible Serum Biochemical Changes in Patients with Hypernephroma." G Winckelmann and J. Wollenweber. (1973, **98**, 1656-1663)—In a majority of 21 patients with hypernephroma a series of biochemical changes, some of them reversible, were found. The changes were unrelated to the presence of metastases and consisted of increased alkaline phosphatase, increased bromsulphthalein retention, increased α_2 globulin, decreased albumin and a decreased Quick value (so-called Stauffer Syndrome). Clotting factors were either unaltered or raised and the fibrinogen level was frequently raised. In 8 patients there were non-specific hepatitis reactive changes. The authors suggest that these biochemical changes though not specific occur sufficiently often to be of some significance in diagnosis.

"The Possibility of arresting Fertility in Men by Drugs." R. Petry and K. Pfizenmayer. (1973, **98**, 1775-1779.)—This is an interesting review of the agents which have been tried in animals and man to control fertility. These include metals, cytostatics, chemotherapeutic agents, hormones natural and synthetic, and a variety of other agents. In addition immunological techniques have had their share of attention but as yet there is no reliable readily reversible technique to recommend. This article is well worth perusal by all interested in this field.

"Phenacetin Kidney." D. Hofflet, D. Bittner, P. Fieghl and H. Kohler. (1973, **98**, 2012-2016.)—In 53 patients 43 females and 10 males over 1 kg of phenacetin-containing drugs had been taken. This was over a period of 20 years and the average intake was 5·8 kg in that time. Anaemia, proteinuria and renal colic were the most important symptoms. Sterile pyuria and haematuria were characteristic and the pyuria often persisted when the patient had stopped taking the drug. If glomerular filtration was greater than 30 ml/min arrest of the disease usually occurred after the drug was stopped. Values between 10 and 30 ml/min were usually accompanied by deterioration and those below 10 ml/min progressed quite rapidly regardless of the drug being stopped. Early diagnosis is of paramount importance.

Journal de Chirurgie

By John Grieve

"Closed Trauma to the Kidney." G. Faure and M. Revol. (1973, **106**, 105-124.)—In 20 years 135 cases of closed renal trauma were treated in the emergency and urological departments of Grenoble Hospital. Over the first 15 years treatment was essentially conservative and late complications were quite frequent. In the last 5 years however radiology and particularly renal arteriography have clarified the situation and permitted planned surgical treatment usually between the 3rd and 10th day. In some instances this has been simple suture, in others partial nephrectomy or heminephrectomy depending on the site of the lesion and the state of the blood supply and finally nephrectomy when the kidney is irretrievably damaged.

"Selective Staining of Parathyroid Tissue during Operations." S. Agugiaro. (1973, **106**, 403-408.)—In a series of experiments in rats, rabbits and dogs the author was able to achieve staining of parathyroid tissue by intravenous injections of toluidine blue. Staining occurs in both the normal parathyroid and the hypertrophied gland. He then applied this clinically and in 10 parathyroid adenomas *in vivo* staining occurred about 30 minutes after injection of dye. In a further 16 patients with normal parathyroids the dye was fixed in 8 but no colour appeared in the other 8. For clinical work the dye is given diluted in 250 ml of physiological saline.

Surgery, Gynecology and Obstetrics

By Thomas Moore

"Effect of Acute Occlusion of the Infrarenal Aorta on Renal Function." Hoke Pollock and George Johnson Jr. (1973, **137**, 805-809.)—The authors at University Hospital, North Carolina, carried out serial controlled observations on 9 males and 3 females for identical periods before, during and after abdominal aortic aneurysmectomy. Induction of anaesthesia caused a fall of the glomerular filtration rate and urinary flow which was not further reduced by clamping of the aorta. Infusion of balanced salt solutions at rates greater than 5·5 ml per square metre per minute caused an increase in glomerular filtration. They believe that adequate infusion prevents an adverse effect on renal function during clamping of the aorta.

"Bilateral Nephrectomy in Patients with Polycystic Renal Disease." Alan H. Bennett, William Stewart, and J. MICHAEL LAZARUS. (1973, **137**, 810-820.)—The authors recount the details of 31 patients suffering from bilateral polycystic renal disease, from a total of 70 such on the dialysis transplant programme at the Peter Bent Brigham Hospital, Boston, who had undergone bilateral nephrectomy. In 24 this was carried out in one stage and in 7 at two separate operations. Of these, 5 were necessitated by unilateral sepsis and 2 to preserve some haematopoietic renal tissue. The remaining kidney was removed 2 weeks and 12 months later, respectively. 16 cases had bilateral nephrectomy before the renal transplant. The authors state that unroofing or decompression of cysts is of no value in these cases and nephrectomy is the best treatment for the complications of haemorrhage and sepsis. In their experience, unilateral nephrectomy always requires eventual removal of the other kidney. The midline transperitoneal approach was regarded as giving the best exposure and they stress the importance of avoiding splenic or adrenal damage.

"Experience with Intensive Surveillance of Urinary Tract Infection." S. GRANT MULHOLLAND, JOHAN N. BRUNN, LEWIS L. CORIEL and WILLIAM S. BLAKEMORE. (1973, **137**, 789-793.)—In the 332-bedded hospital in Pennsylvania, acquired urinary infections were recorded by the attending physicians. The appointment of a special Hospital Infections Nurse to seek out these cases and finally the availability of a computer for collection and recording of data has shown an increase of 16·7% of the cases so affected. During 1 year 12% of the admitted patients had 1,119 urinary tract infections two-thirds of which were hospital acquired. Bacteriological studies showed significant differences in the causative organisms in the 2 groups.

"Ex Vivo Perfusion, Arteriography and Autotransplantation Procedures for Kidney Salvage." J. L. CORMAN, J. T. ANDERSON, J. TAUBMAN, D. P. STABLES, C. G. HALGRIMSON, M. POPOVTZER, and T. E. STARZL. (1973, **137**, 659-665.)—This is a very interesting paper from the well-known Clinic in Denver, Colorado. Details are given of 3 patients suffering from arterial disease causing hypertension. In 2, a kidney with its vascular supply and a length of ureter was removed and in 1, the vascular supply was divided but the ureter left intact; the kidneys were then perfused by the Belzer technique. During the extra-corporeal perfusion, the kidneys were studied, dissected and repaired and then returned to the patients by the standard extra-peritoneal techniques in the iliac fossae. Very good results were obtained. The authors stress that this technique is only necessary in the most difficult cases of arterial disease, the orthodox methods being usually sufficient. They also mentioned the possibility of using the method for other lesions, *e.g.* malignant disease.

"Multiple Primary and Segmental Renal Artery Revascularization utilizing Autogenous Saphenous Vein." CALVIN B. ERNST, JAMES C. STANLEY and WILLIAM J. FRY. (1973, **137**, 1023-1026.)—The authors describe their techniques for using free portions of saphenous vein as grafting material for reconstructing multiple primary renal arteries and proximal segmental vessels. Microvascular techniques facilitate the performance of these difficult anastomoses. They quote cases showing efficient revascularization of ischaemic kidneys by it.

"Renal Artery Stenosis and Azotemia." JOSEPH F. KAUFMAN. (1973, **137**, 949-955.)—This well-known author from the University of California School of Medicine in Los Angeles reports four cases suffering from renal artery stenosis, hypertension and moderate uraemia in whom he performed re-vascularization of the kidney. Improvement was complete in two young patients and incomplete in two older patients. Severe uraemia is unlikely to occur as a result of renal artery stenosis alone. However, some patients with a moderate degree of renal failure with or without renal parenchymal disease can be benefited by procedures to restore or improve renal blood flow.

"Technical Improvement in Saphenous Vein Arteriovenous Fistula for Hemodialysis." F. HARDER and F. ENDERLIN. (1973, **137**, 1017.)—In the thigh the proximal end of the divided vein can be anastomosed end to side to the superficial femoral artery and the arterialised vein used for hemodialysis. Alternatively, a segment of vein may be removed from the thigh and used in the forearm to bridge obstructions in arteries or veins.

"The Diagnosis and Treatment of Hyperparathyroidism after Renal Homotransplantation." W. P. GEIS, M. M. POPOVYZER, J. L. CORMAN, C. G. HALGRIMSON, C. G. GROTH and T. E. STARZL. (1973, **137**, 997-1010.)—Ninety of the several hundreds who had received renal homotransplants in this well known centre in Denver Colorado, at periods from weeks to ten years later, were screened by the usual diagnostic techniques, including estimation of the ionized serum calcium for the presence of hyperparathyroidism. The diagnosis was confirmed in 18 cases. All but one had bone disease or metastatic soft tissue calcification. Histological examination confirmed the presence of diffuse parathyroid hyperplasia in all cases. Nine were treated by standard subtotal parathyroidectomy and nine underwent total parathyroidectomy with a portion of one gland being implanted into the subcutaneous tissue. The weight of excised parathyroid tissue varied from 200 to 2,300 mg. Before operation 15 of the cases were treated with oral phosphorus supplement. This reduced the total serum calcium but did not affect the serum ionized calcium. Profound hypocalaemia always occurred just after autotransplantation with 100% tubular phosphate reabsorption; calcium supplementation was required and gradually decreased or discontinued after two to six months. Only one patient had significant hypoparathyroidism. After subtotal parathyroidectomy there were no examples of hypoparathyroidism but there has been one example of recurrent hyperparathyroidism. They also stress the importance of estimation of the ionized serum calcium estimation in the diagnosis of the condition and the harmful effect of hypercalcaemia on the kidney.

"Changing Patterns in Hyperparathyroidism." EUGENE W. FRIEDMAN, ARTHUR E. SCHWARTZ and RONALD H. SPIRO. (1973, **137**, 941-944.)—The authors from the Mount Sinai School of Medicine University of New York report a detailed analysis of 134 operations performed on 131 patients thought to be suffering from primary hyperparathyroidism. Apart from the 12 in whom the diagnosis was incorrect all but 16 were cured of their hypercalcaemia by the procedure. Bone disease or renal stones was the reason for the procedure in most of the early cases. In recent years the number of cases has gradually increased and most patients have asymptomatic hypercalcaemia found on a biochemical survey. Hypercalcaemia was the only reliable diagnostic finding. In 192 patients adenoma of the parathyroid was the cause and in four of these, two glands were involved. In 16 cases the abnormal gland was in the mediastinum but in all but four it was easily removed from the ordinary thyroid incision. In four cases it was in the lobe of the thyroid. Because of this finding the authors advise that in cases where only one parathyroid gland is recognised on the one side then that lobe of the thyroid should be removed in preference to splitting the sternum and looking in the mediastinum. In 16 patients the pathological change in the parathyroid was diagnosed as hyperplasia. The authors stress the difficulty in distinguishing adenoma from chief cell hyperplasia and emphasise the importance of identifying all four parathyroids and of sending a portion of at least one other gland for pathological investigation in addition to the one thought to contain an adenoma.

Der Urologe

By John Grieve

"The Classification, Course and Treatment of Penile Carcinoma." P. Lichtenauer, E. Ott and K. H. Dröge. (1973, **12**, 66-70.)—The authors review 317 cases of penile carcinoma collected from German urological clinics. Of these 38% had phimosis. All tumours were squamous cell carcinomata of varying differentiation and usually affected the glans. Metastases were more common in poorly differentiated tumours. Radiation had been used in many of the patients and despite the relative insensitivity of the tumours to radiation the authors recommend that radiation should be given whether lymph glands are involved or not. Some cases were treated by radiation alone and other by combined surgery and radiation. The best results were in those treated before palpable lymph glands appeared and in whom the tumour was well differentiated.

"The Value of Percutaneous Renal Biopsy in Chronic Pyelonephritis." W. Schreiber. (1973, **12**, 13-27.)—In this investigation from Nürnberg, percutaneous renal biopsy was helpful in determining the extension of the pathological process in the renal parenchyma. Of 93 patients examined in this way 49 showed minimal changes while 44 had the typical changes of interstitial nephritis. Among the 49 with minimal changes 23 had bacteriuria and in the 44 with pathological changes 26 had bacteriuria. When biopsy material was cultured 3 of the first group and 4 of the second showed bacterial growth. When the urine was sterile there was no growth from the biopsies. There is therefore a considerable discrepancy between the pathological findings in the kidney and the bacteriological findings in the urine.

Rozhledy V Chirurgii

By J. V. Mandel

"Better Function of the Female Urethra after Plastic Operations using the Bulbospongiosus Muscle." V. Šebek. (1973, **53**, 1: 47-51.)—The author did five plastic operations on the female urethra, and considers it best to support the new urethra by the bulbospongiosus muscle, in order to achieve urinary continence. Urinary continence was achieved in a patient suffering from total hypospadia. Reconstruction of a urethra destroyed by injury was not successful. Four of the patients were failures from previous operations.

"Neoplasms of the Female Urethra." V. Šebek. (1974, **53**, 47-51.)—Based on his experience of five operations for neoplasms of the female urethra the author considers it best to support the newly formed urethra by bulbocavernous muscle, in order to achieve perfect urinary continence. In a patient suffering from hypospadia (and cleft symphysis) repair was done according to the method of Pawlik-Dudley. He tried the same method in a patient whose urethra was destroyed by injury but he was not successful. Four women were operated on previously without success.

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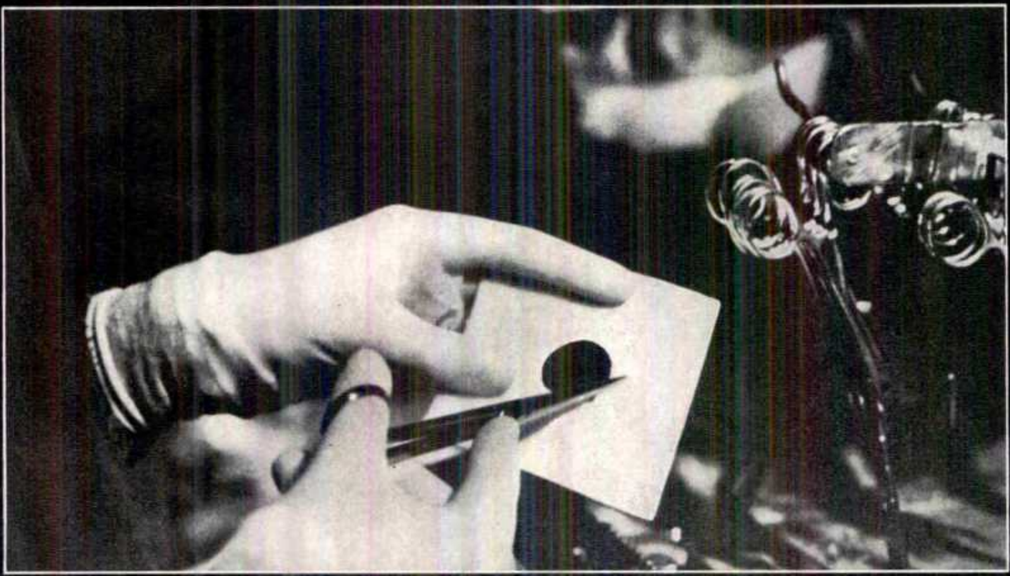

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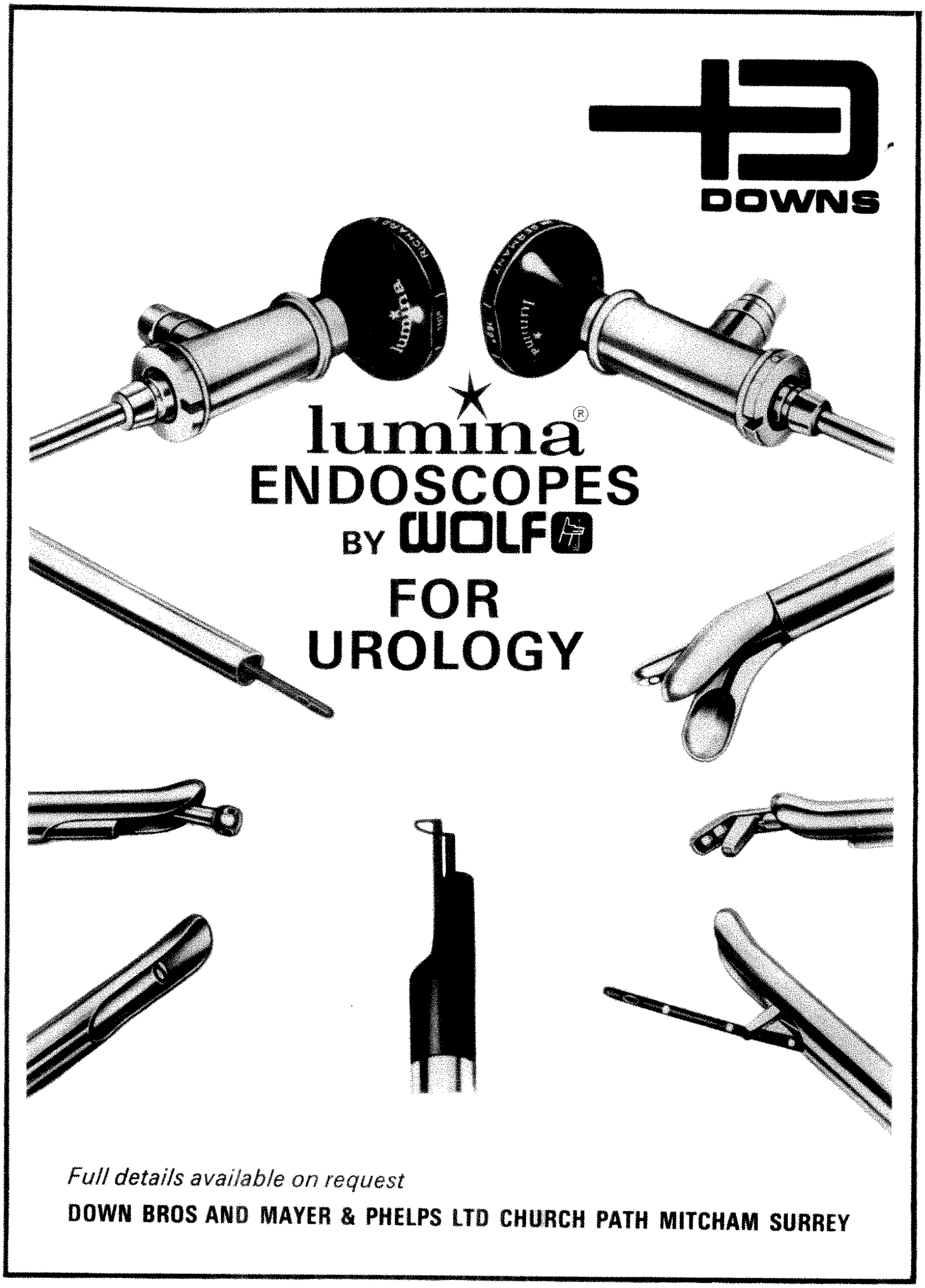

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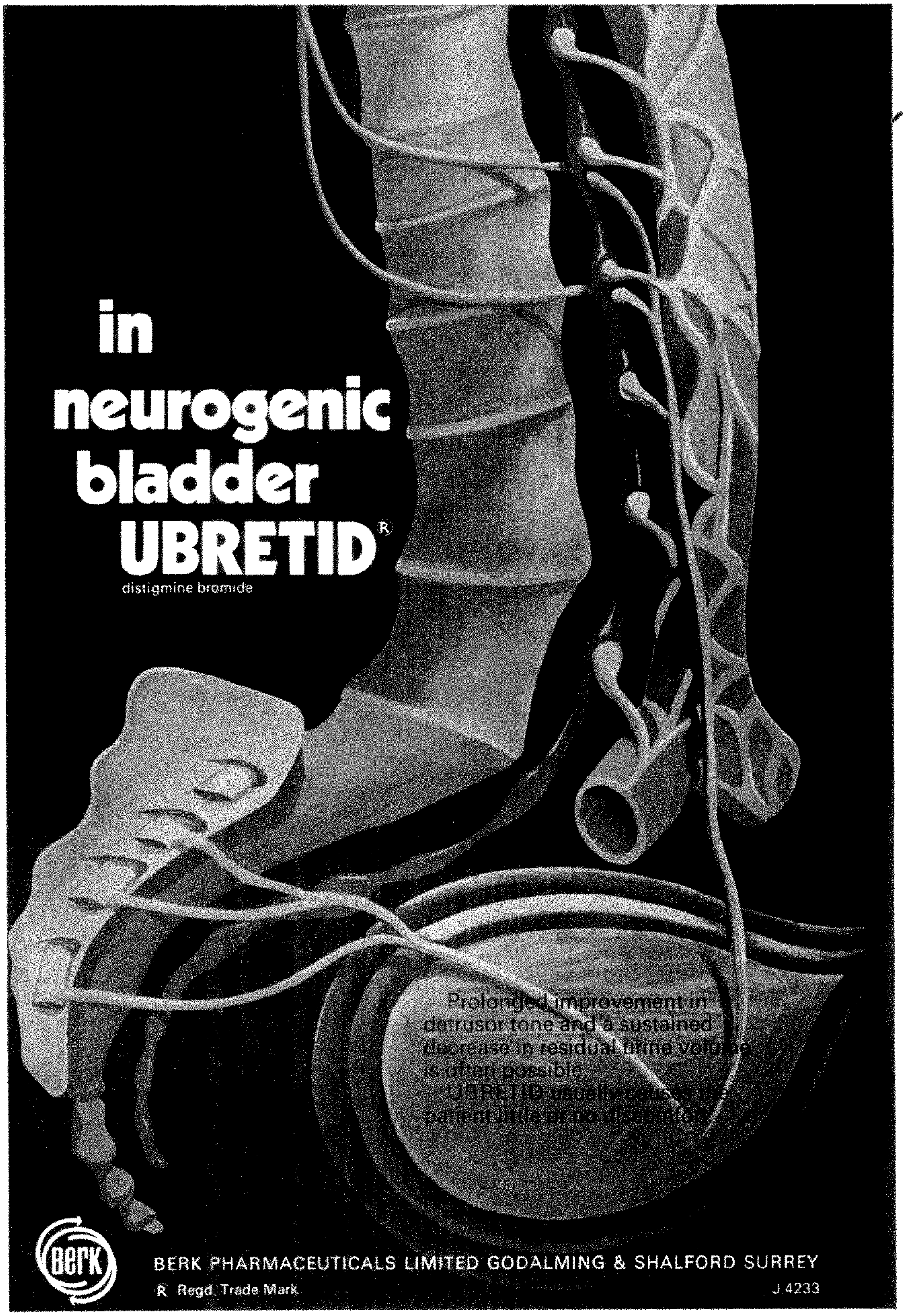

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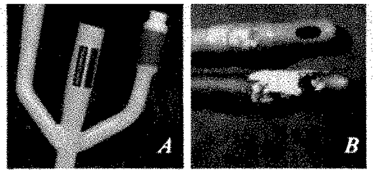

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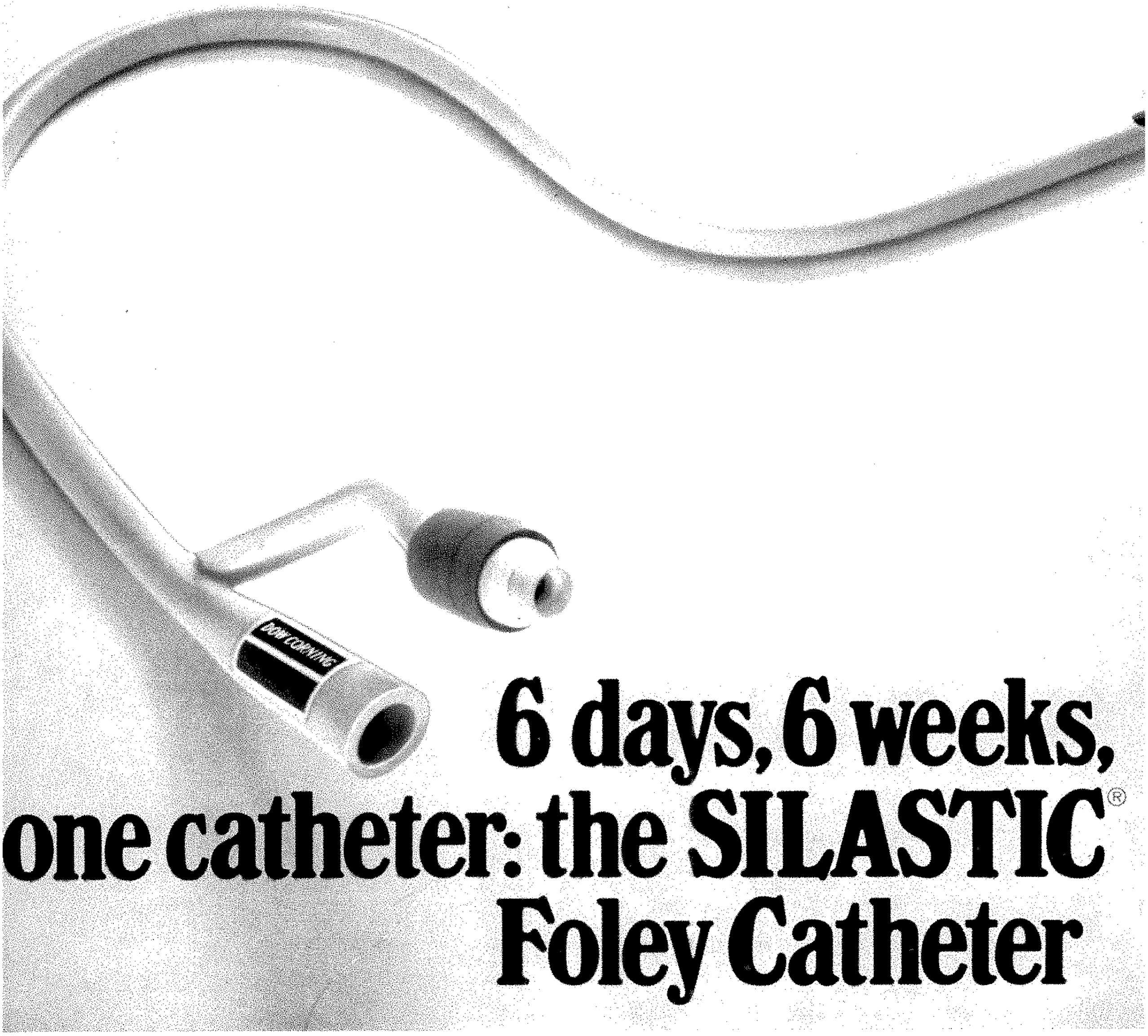

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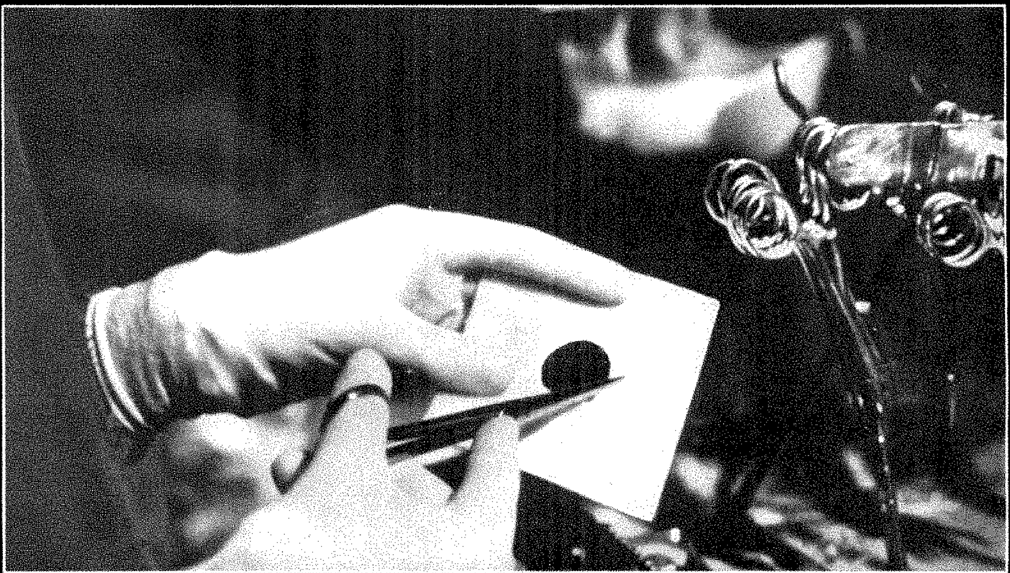

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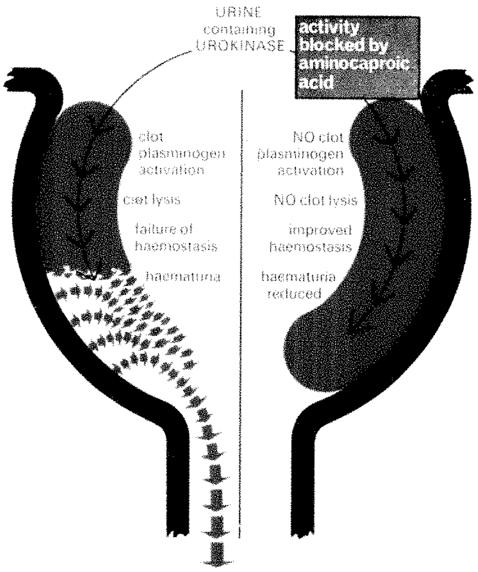

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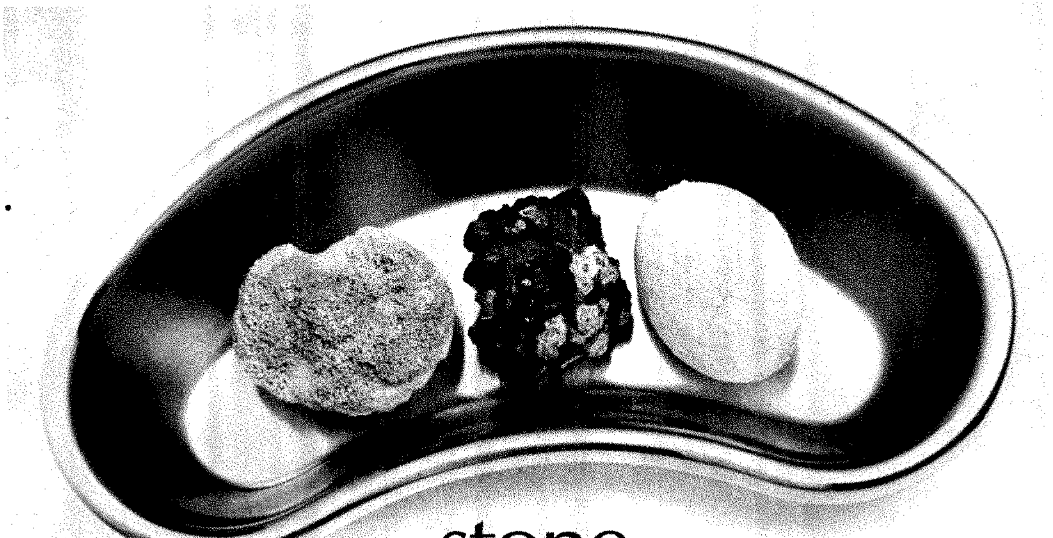

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1. Amer J Med. (1971) **50**, 67-76.
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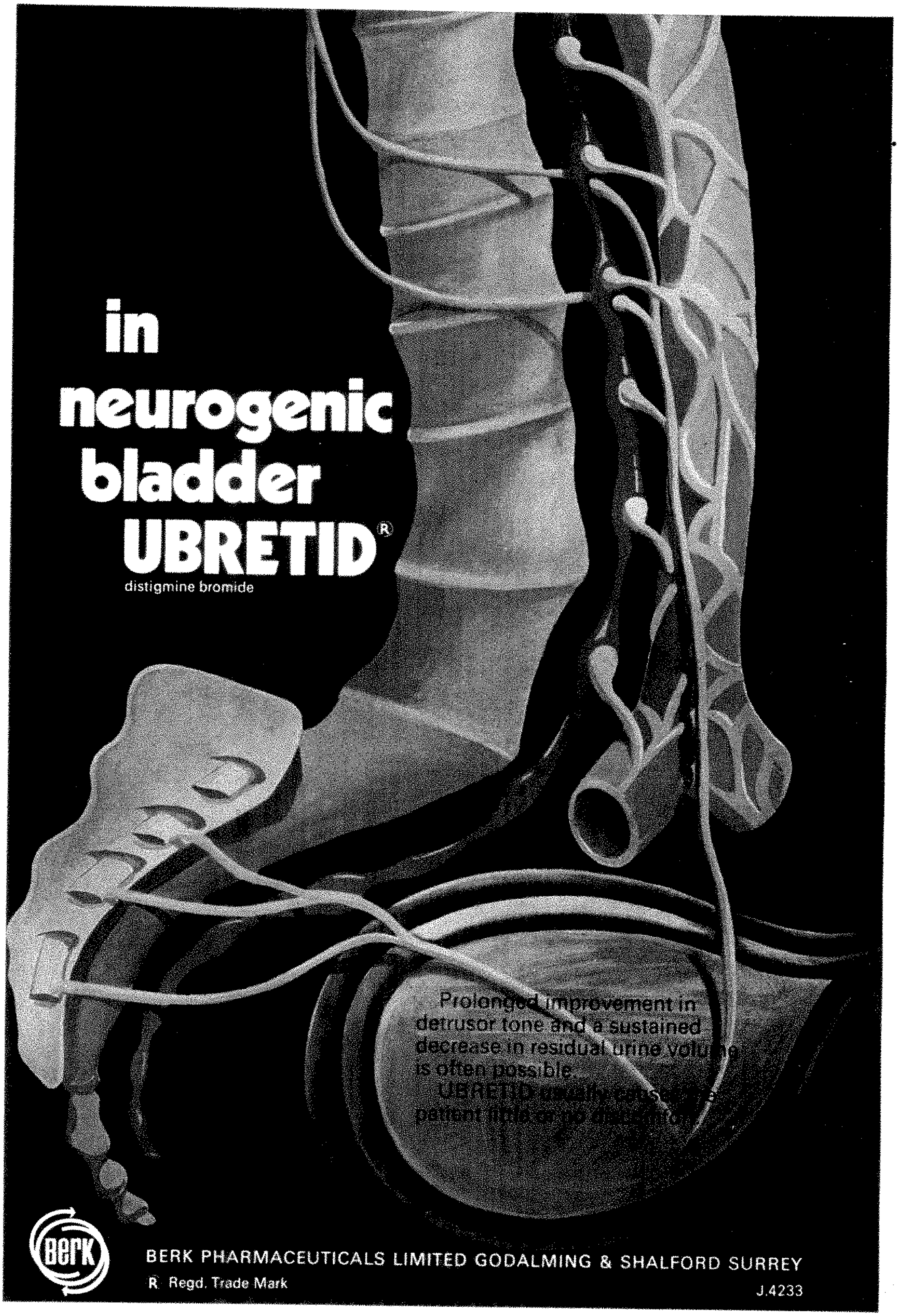

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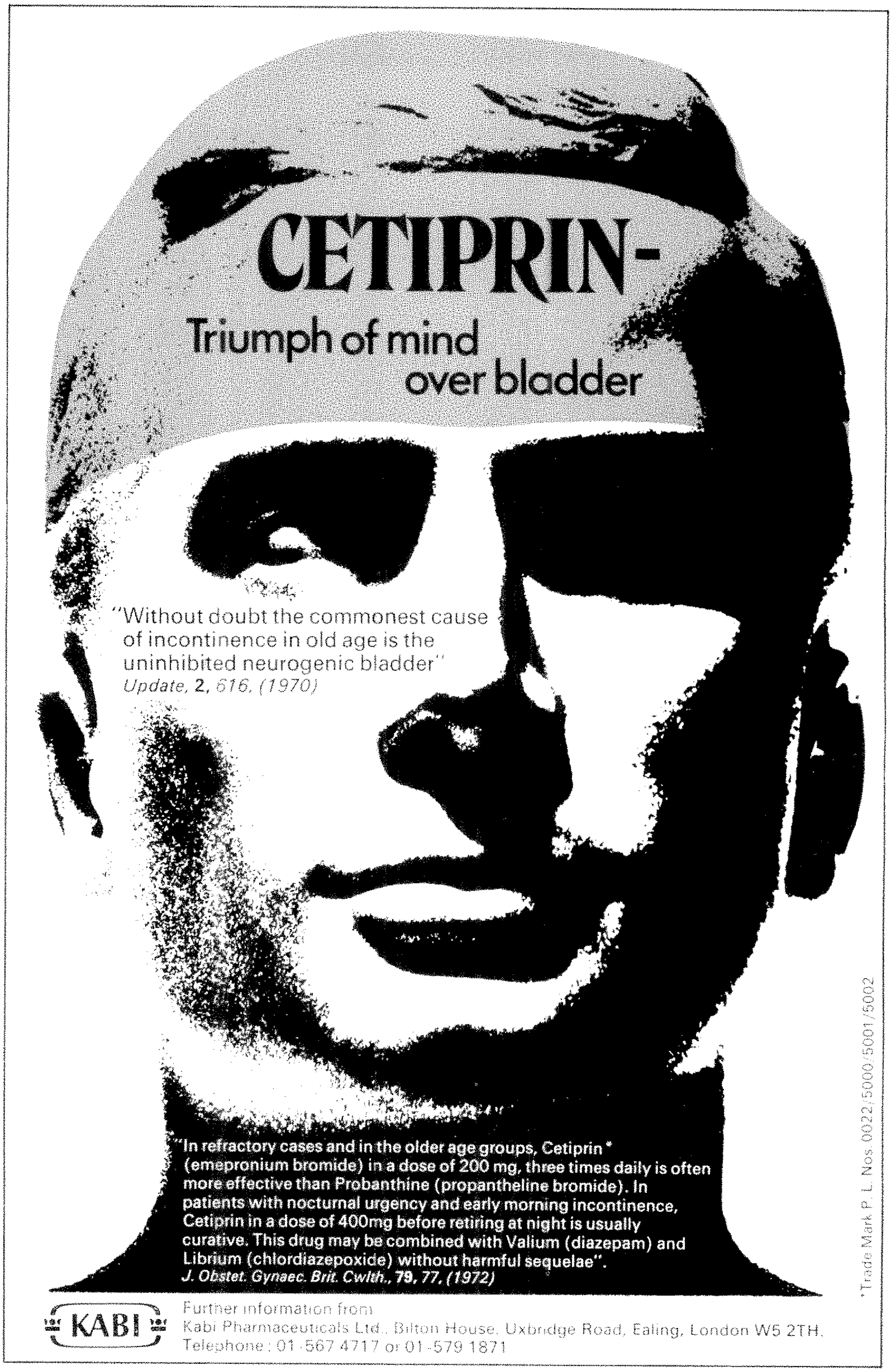

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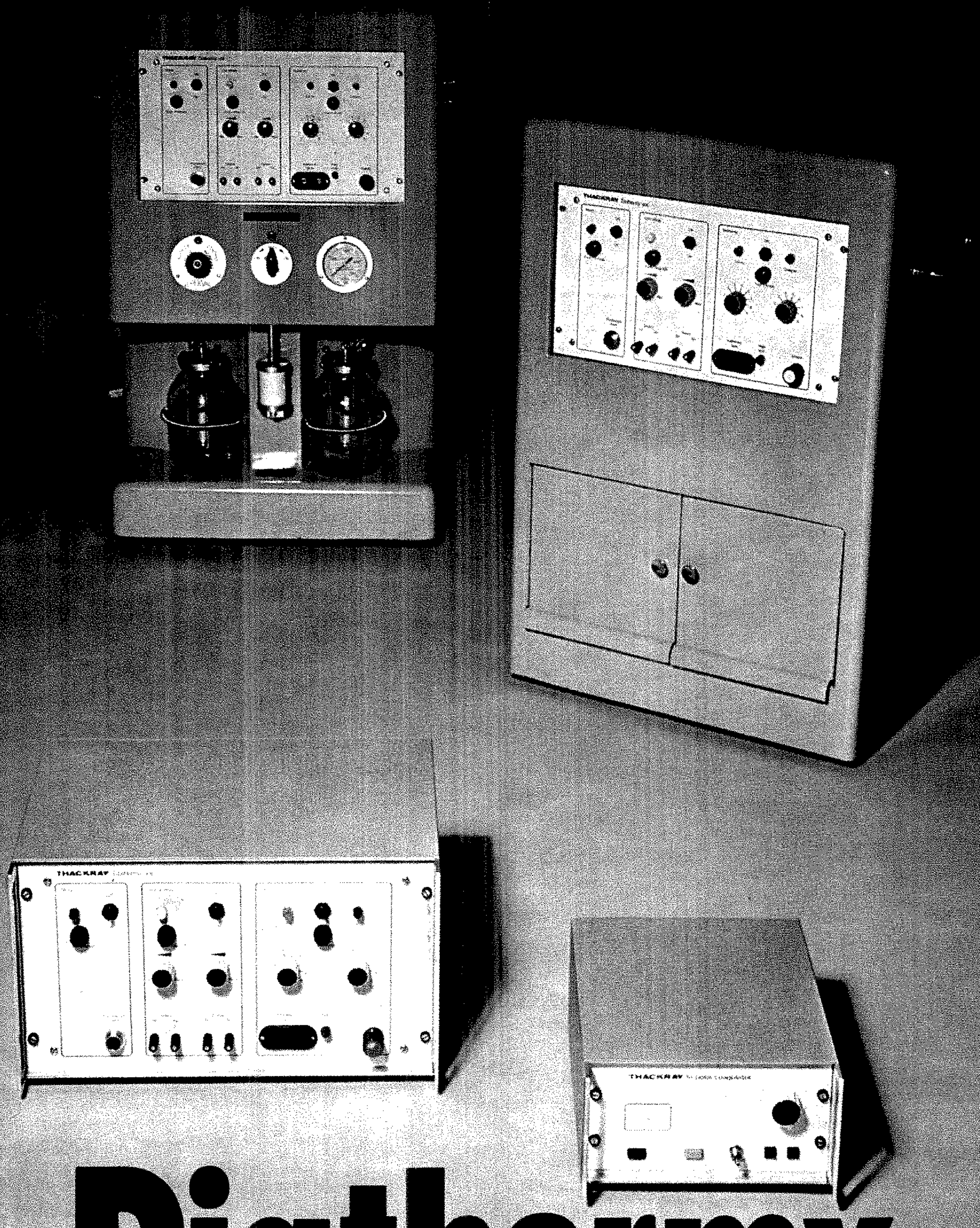

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British Journal of Urology (1974), **46**, 481–484

Renal Angiomyolipoma—Report of 5 Cases

MICHAEL KIN GAY MA and KEENG WAI CHAN

Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

Angiomyolipoma was first described by Bourneville in 1880. It is a rare tumour affecting the kidney. Pathologically it has been classified as a hamartoma with no evidence of malignant changes. However, clinically it often mimics a malignant renal lesion and is treated as such. It may occur as part of the complex of tuberous sclerosis and in such cases the lesion is usually bilateral and the diagnosis made without much difficulty. It is only when it occurs alone that it becomes a diagnostic problem. The purpose of this paper is to present 5 cases seen in Hong Kong and to review the clinical manifestations of this latter group of angiomyolipoma.

Up to 1959, only 16 confirmed cases of renal angiomyolipoma occurring in otherwise normal individuals were collected from the literature by Klapproth and co-workers. He also presented 4 more from his own series. Since then several authors have written about this condition and added more cases to the collection. Price and Mostofi (1965) reported 30 cases of symptomatic renal angiomyolipoma from the files of the Armed Forces Institute of Pathology and the Kidney Tumour Registry of the American Registry of Pathology. Long and Lynch (1971) presented 1 case with hypertension which resolved after nephrectomy. McCullough, Scott and Seybold (1971) collected 7 cases of which 4 had no feature of tuberous sclerosis. They all underwent nephrectomy because of significant symptoms. In their case report of a woman presenting with pain and haematuria, Silbiger and Peterson (1971) discussed the angiographic features of this tumour. Weisler and Lakey (1971) reported 1 case for which they had to perform an emergency left nephrectomy for a bleeding angiomyolipoma.

In a few patients, the tumour was an incidental autopsy finding. Farrow *et al.* (1968) in his clinicopathologic study of 32 cases discovered 5 such cases. We have seen 5 patients with angiomyolipoma during the last 4 years. Three were symptomatic while the other 2 were accidental findings. One was discovered during an exploration for a bleeding gastric ulcer and in the other while carrying out a postmortem examination for a ruptured aortic aneurysm.

Case Reports

Case 1. A 38-year-old Chinese housewife was admitted as an emergency in January 1972 with painless haematuria and suprapubic distension. On examination, the right kidney was palpable and the bladder distended. She was afebrile and her blood pressure 110/70 mm Hg. Pleural effusion was detected on the right side which on tapping yielded 600 ml of straw-coloured fluid.

Emergency cystoscopy showed the bladder was full of blood and clot. After evacuation of the clot, the right ureteric orifice was found to be oedematous but the rest of the bladder was normal. Excretory pyelography showed an enlarged right renal outline with dilated upper and lower calyces. The left kidney was normal. Right retrograde pyelogram showed more clearly the stretched and distorted right upper and lower calyces with a radiolucent filling defect at the pelvi-ureteric junction (Fig. 1).

Renal angiogram demonstrated a large cystic mass with multiple new vessels and arteriovenous shunting. Tumour staining and extrarenal spread were evident (Fig. 2). At operation, a solid tumour, 5 cm in diameter, was found in the lower pole of the right kidney. The renal vein was clear and no enlarged lymph nodes were found. Nephrectomy was performed. The postoperative course was uneventful.

The specimen measured 12 × 8 × 5 cm. The cut surface showed yellowish greasy-looking tissue with areas of haemorrhage and small quantity of compressed renal tissues. The calyces were dilated and the pelvis chronically inflamed.

Case 2. A 48-year-old Chinese nursing sister was first seen in August 1971 with a history of right upper quadrant pain for 3 days. It was colicky in nature and each time lasted several hours. There was concomitant dizziness and on one occasion she fainted. Examination revealed a tender palpable right kidney. B.P. 150/110.

Intravenous pyelography and retrograde pyelogram showed a mass at the lower pole of the right kidney. Surgical exploration revealed a tumour situated at the lower pole of the right kidney which was adherent to the overlying peritoneum. No regional lymph nodes were found. Right nephrectomy was done with removal of the perirenal fat. Postoperative course was uneventful. B.P. 140/90.

The specimen contained ill-defined nodular areas varying from a few mm to 6 cm in diameter at the lower pole, replacing all the normal renal tissue. The colour varied from pale to yellowish, with greasy appearance. There were patchy areas of haemorrhage in the larger nodules. A normal looking renal parenchyma was present in the upper pole. The tumour nodules were adherent to the renal capsule, but extracapsular invasion was not evident.

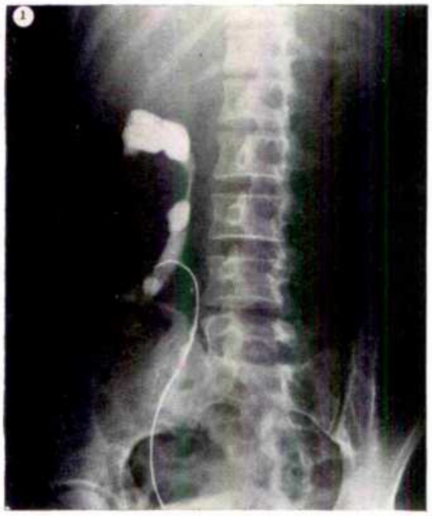

Fig. 1. Case 1. Right retrograde pyelogram.

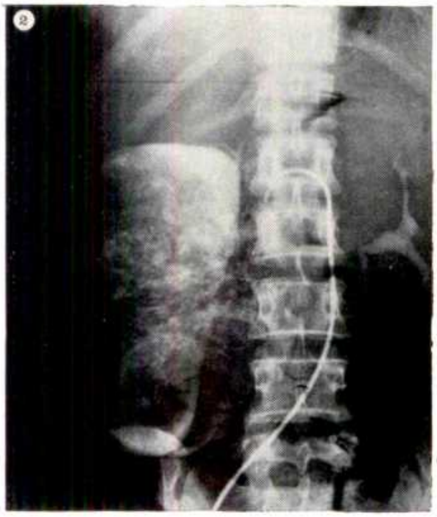

Fig. 2. Case 1. Right renal angiogram.

Case 3. A 61-year-old Chinese woman who had on and off epigastric pain for 1 year was admitted to hospital with severe haematemesis on 28th April 1971. B.P. 130/80. Emergency laparotomy revealed a chronic gastric ulcer and a partial gastrectomy was done. On further exploration, a subcapsular nodule, 2 cm in diameter, was found in the mid-zone of the left kidney. This was excised and the postoperative course of the patient was uneventful. B.P. 120/90 Cut section of the nodule showed a yellowish greasy surface with no encapsulation.

Case 4. A 63-year-old Chinese female patient underwent appendicectomy in 1959. Between 1956 and 1959, she passed 2 renal calculi. In 1963, she was found to have carcinoma of the left breast for which a radical mastectomy was done. There was no positive axillary lymph node. In the same year, she developed symptoms of gall bladder disease and investigations showed presence of gall stones. Intravenous pyelography and right retrograde pyelography also showed stones in lower calyces of the right kidney. The kidney was displaced upwards, laterally and anteriorly. In 1969, she had acute upper abdominal pain and a further intravenous pyelogram showed findings similar to those in 1963. Repeated urine examinations showed only occasional pus cells and red blood cells. B.P. 190/100. She was explored and a cystic swelling, 3½ × 4 × 8 cm, was found in the hilum of the right kidney. Right nephrectomy was done and the patient recovered well. She was last seen in 1972, alive and well with a normal chest X-ray. B.P. 150/90.

Section of the kidney showed that the cystic cavity contained abundant blood clots. There were a few ill-defined areas of greyish white tissue, 1 cm in diameter in the renal parenchyma adjoining the above-mentioned cavity, fatty tissue and blood clots.

Case 5. A 71-year-old Chinese male collapsed suddenly on level ground with loss of consciousness, convulsion and incontinence of urine. He died on arrival to hospital. He was a known hypertensive for 10 years.

Postmortem examination revealed dissecting aneurysm of aorta with haemopericardium. A subcapsular nodule, 1 cm in diameter, was present on the left kidney. Section of this showed a yellowish greasy surface without encapsulation.

Histological Study of the 5 Cases

Blocks were taken from representative parts of each tumour, including the adjacent normal-looking renal parenchyma. Paraffin sections were stained with haematoxylin and eosin, Verhoeff van Gieson and phosphotungstic acid-haematoxylin. Frozen sections were stained with oil red O for fat.

The microscopic appearances of these growths are distinctive and present no difficulty in diagnosis. The features noted in these 5 cases are similar to those previously described in the literature and consisted of the following 3 components: (1) Adipose tissue. (2) Smooth muscle bundles and (3) Thick-walled blood vessels.

Among the fatty tissues, there are irregular masses of smooth muscle cells and abnormal blood vessels. The former tends to arrange haphazardly in interlacing bundles. Their nuclei are rounded, ovoid or elongated with coarse to vesicular chromatin pattern, and more plump in the cellular areas. These smooth muscle cells merge with the external layer of the blood vessel walls.

The majority of the blood vessels are tortuous and vary from 36 to 270μ in diameter. Their lumens contain well preserved red blood cells. The walls range from 10 to 108μ in thickness and compose of varying amount of smooth muscle and collagenous fibres. A few vessels exhibit frayed internal elastic lamella and in others only fragmented elastic fibres are seen in the vessel walls. There are also scattered small foci of condensed elastic tissue among the collagenous fibres in the stroma adjoining these vessels.

In cases 2 and 4, there are small isolated remnants of degenerated renal parenchyma intermixed with the 3 components mentioned above. These are not seen in the other 3 cases.

Comments

It has been shown by various authors that most angiomyolipoma occurring in patients without tuberous sclerosis are symptomatic. 57 cases were collected in the literature, they were reported by authors mentioned above and others including Brody and Lipshutz (1955), Heckel and Penick (1948), Hulse and Palik (1951), Le Brun, Kellett and Macalister (1955), Morgan, Straumfjord and Hall (1951), Rusche (1952), Taylor and Genters (1958), Tweeddale *et al.* (1955) and Weaver and Carlquist (1957).

96·5% presented with some symptoms that require medical attention. The rest are incidental findings during laparotomy or at postmortem examination. A summary of the analysis is shown in Table I.

Table I

Clinical Features of 57 Cases of Angiomyolipoma.

	Number of Patients	Percentage
Pain	42	73·7
Haematuria	15	26·3
Infection	6	10·5
Hypertension	1	1·8
Loin mass	24	42·1

The age of the affected patients ranged from 12 to 71, with the peak incidence in the 5th decade of life. Among the 57 patients analysed, there are 45 females and 12 males with a female preponderance of 3·8 times over the male.

Pain is by far the most common presenting symptom (73·7%). It is usually reported as loin pain of a few hours duration. Occasionally, it is associated with haematuria of varying degrees. The cause of pain is probably due to haemorrhage inside the tumour. Two of our 5 cases presented with pain in the flank, and in each of the nephrectomy specimen areas of extensive haemorrhage were found. The contrary seems to hold true because areas of haemorrhage were absent in symptomless cases.

Haematuria occurred in 15 cases (26·3%). In some patients it might lead to shock and required emergency surgery. A palpable kidney was found in 24 cases; most of them were associated with loin pain.

Investigations done in these cases included intravenous and in some retrograde pyelography.

Unfortunately the findings were non-specific and could not be distinguished from a malignant renal lesion. Renal angiogram probably would be more diagnostic. As pointed out by Silbiger and Peterson (1971), the network of tortuous small vessels which was part of the basic pathology were usually clearly shown. Also, these arterial networks persisted for some time with little sinusoidal and venous vascularity. With more experience and wider application of renal angiography, most of these hamartomas could be correctly diagnosed. In such case, a simple excision could have been carried out as in each patient the tumour had been shown to be benign.

Summary

Five cases of unilateral renal angiomyolipoma seen in Chinese patients in Hong Kong are reported.

The clinical manifestations are reviewed in 57 cases which included 52 collected in the literature. The predominant features are pain (73·7 %), haematuria (26·3 %) and the presence of a loin mass (42·1 %).

Among various investigative procedures, renal angiogram is probably the most useful.

We would like to thank Professor G. B. Ong, Dr T. B. Teoh and Dr K. T. Tham for their kind assistance in the study of these cases.

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Renal Angiomyolipoma Causing Hypertension: A Case Report

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A renal angiomyolipoma presenting with hypertension, with lowering of the blood pressure by nephrectomy is reported. The possible causes for hypertension are discussed.

Case Report

A 47-year-old physician's secretary was found to have asymptomatic hypertension.

Physical examination revealed her blood pressure to be 170/105 to 190/130 over 5 days observation in hospital. There was no abdominal mass or bruit.

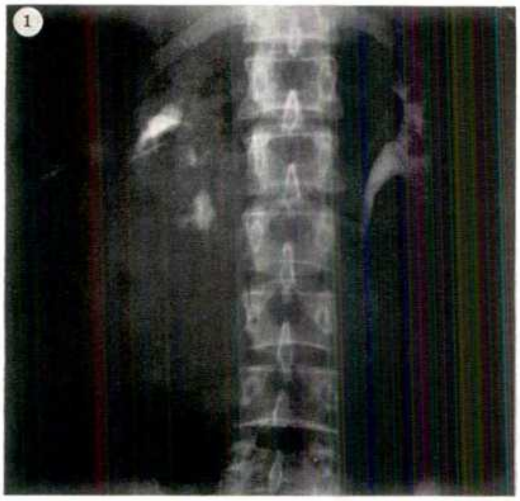

Fig. 1. Intravenous pyelogram showing space occupying lesion at lower pole of right kidney.

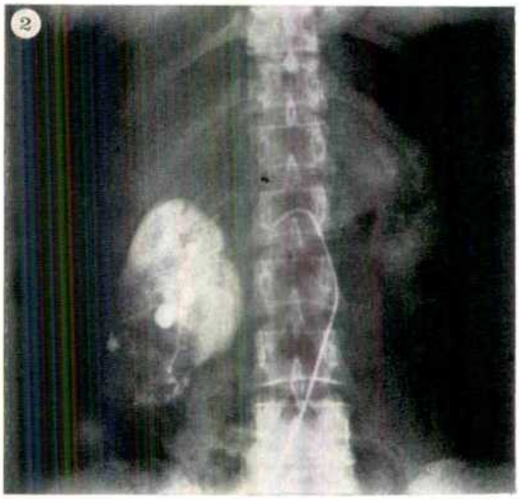

Fig. 2. Renal arteriogram showing neovascularity and intrarenal aneurysm in renal mass.

Her urine was normal microscopically, was sterile on routine and tuberculous cultures. Urinary cytology was normal. Intravenous pyelography and infusion pyelograms with tomography showed a space occupying lesion in the lower half of the right kidney (Fig. 1). Aortography and selective right renal angiography showed hypervascularity, with tortuous abnormally distributed vessels throughout the lesion. There was aneurysmal dilatation of an intrarenal artery (Fig. 2).

Full blood count and erythrocyte sedimentation rate were normal. Serum creatinine and blood urea nitrogen were normal; 24-hour creatinine clearance was 90 ml/min. Liver function tests, blood glucose and electrolytes were normal.

The patient's blood volume was 5·15 litres, the expected volume for her height and weight was 4·42 litres.

The plasma renin activity, on a general diet resting in bed was 1·02 ng/ml/hr; the renin activity from the right renal vein was 2·27 ng/ml/hr from the left 1·72 ng/ml/hr; a ratio of 1·3:1. (These figures are at the upper limit of normal for our laboratory.)

Through a Nagamatsu incision the right kidney perirenal fat and Gerota's fascia were removed *en bloc* after early pedicle ligation. Her postoperative course was uneventful; after 1 week her blood pressure was 170/100 and the plasma renin activity 0·32 ng/ml/hr. One year after surgery, the blood pressure is 150/80 to 160/90 without medication.

The lower pole of the kidney was replaced by a yellow-brown tumour that did not have any obvious capsule. Histology showed it to be an angiomyolipoma, being composed of blood vessels, fat and fibromuscular tissue (Fig. 3).

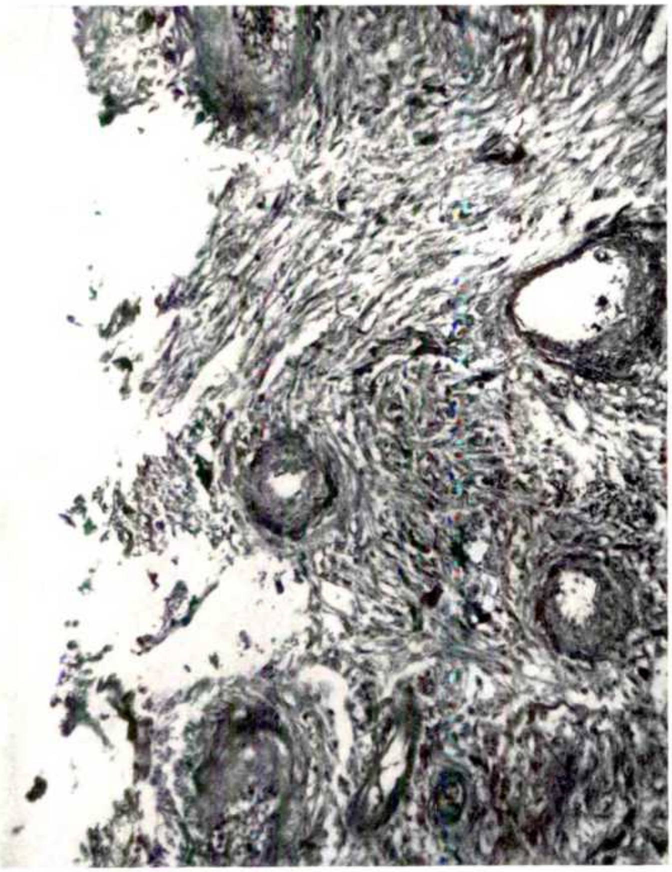

Fig. 3. Photomicrograph of lesion showing numerous abnormal arterioles and areas of fat in fibromuscular tissue. H & E × 20.

Comment

An association between renal tumours and hypertension has been recognised for many years; Chisholm and Roy (1971) recently reviewed the possible mechanisms for this.

In this case there was no angiographic evidence of main renal artery involvement or external compression by the lesion. The kidney tissue adjacent to the tumour may be compressed within the renal capsule and be rendered partially ischaemic.

The plasma and renal vein renin activity levels were at the upper limit of normal for our laboratory. The renin activity from the affected side was 1·3 times greater than the contralateral normal side. A ratio of 2:1 is generally considered as significant in renal vascular hypertension. However in renal vascular lesions the total renal blood flow is reduced whilst in a vascular tumour it is increased thus the total renin secretion is probably much greater than as reflected by the ratio found. The fall in plasma renin activity after nephrectomy is considered significant.

McCullough, Scott and Seybold (1971) reported 7 cases of renal angiomyolipoma: 2 were hypertensive—1 had associated tuberous sclerosis and polycystic disease, the other had mild hypertension but was incompletely investigated. Their review of the literature on angiomyolipoma revealed 2 other cases associated with polycystic disease and hypertension in adults.

We were unable to find any other reports of hypertension associated with angiomyolipomata in the absence of tuberous sclerosis.

Summary

A patient with asymptomatic hypertension due to a renal angiomyolipoma is described. The possible causes for hypertension, in particular increased renin secretion is discussed.

We would like to thank Dr G. R. I. Powers and Dr E. Liepa of the Department of Radiology and Pathology.

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Sodium Cellulose Phosphate in Vitamin D Intoxication

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Cases of hypercalcaemia due to vitamin D intoxication still occur due to unawareness of the possible dangers of such treatment and the need to monitor the serum calcium level and renal function in patients receiving this therapy.

Case Report

A 50-year-old male, manager of a wholesale grocery store was admitted on the 24th November 1970, to his local hospital, complaining of progressive nausea, anorexia, vomiting, thirst, polyuria, nocrutia and weight loss for the previous twelve months. Mental confusion had been noticed by his wife a few days prior to admission. His investigations had included a normal blood urea level (32 mg/100 ml), when first seen, which had increased to 72 mg/100 ml during observation. His serum calcium level was found to be 14·2 mg/100 ml. It was discovered that intramuscular injections of Gewo[1] GT50 A and B which had been prescribed for the treatment of osteoarthritis of the hips by a practitioner (not the patient's usual doctor) contained 500,000 I.U. of calciferol in each ampoule. Over the past 5 years he had received 2 injections of preparation "A" and 1 of preparation "B" every 5 weeks, *i.e.* a total of approximately 78 million units of calciferol. His other therapy had consisted of indomethacin, norgesic and 6 months of oral iron. Following the diagnosis of vitamin D intoxication he had been started on prednisolone 60 mg daily reducing by 5 mg/day to 30 mg daily before transfer to the Liverpool Regional Urological Centre on 11th January 1971. On transfer, he was wasted, dehydrated and agitated. Pulse regular 84/minute. Blood pressure 190/150. Examination of the chest, heart, abdomen, fundi and rectum proved normal. Muscle tone and tendon reflexes were also normal. Both his hip joints were severely osteoarthritic. Slit lamp examination revealed calcium deposits in the periphery of both corneae.

Investigations$_2$ Haemoglobin 11·6 g/100 ml. Blood film: Normochromic normocytic red cells. E.S.R. 35 mm in 1 hour. M.S.U. trace of protein, W.B.C. 10/HPF, culture sterile. Blood urea: 100 mg/100 ml. Na 134 mequ/l, K 3·5 mequ/l, Cl 97 mequ/l, CO_2 28·5 mequ/l. Serum creatinine 2·8 mg/100 ml. Creatinine clearance 33 ml/min. Serum calcium 15·6 mg/100 ml. Serum inorganic phosphorus 3·6 mg/100 ml. Serum alkaline phosphatase 13·0 K.A. units/100 ml. Urinary calcium excretion 560 mg/24 hours. Chest X-ray: normal. There was radiological evidence of calcification in the aorta and iliac arteries but none in periarticular tissues or muscles. Daily urine volumes varied from 2½ to 3½ l.

Progress: He was started on a 40 g protein diet containing not more than 250 mg calcium daily. Prednisolone 30 mg/day was continued and Whatman's sodim cellulose phosphate 5 g 3 times daily was added on the 4th day. On this treatment the serum calcium and 24 hours urinary calcium content dropped to 12·8 mg/100 ml and 290 mg respectively by the 13th day. On the 12th day of treatment we ran out of sodium cellulose phosphate for a week due to a postal strike and the opportunity was therefore taken to monitor the effect of cessation of sodium cellulose phosphate therapy on the serum and urinary calcium levels. It was found that omission of sodium cellulose phosphate resulted in a rise of urinary calcium output to an average of 630 mg/day (Fig. 1). During this period there was only a small rise in the serum calcium.

He was mentally fit when discharged home on 13th February on a normal protein diet containing not more than 400 mg calcium per day, sodium cellulose phosphate 5 g three times daily and prednisolone 15 mg/day. He resumed part-time work in April 1971 and full time work in August 1971. Prednisolone was gradully decreased by 2.5 mg per day every 3 months and cellulose phosphate reduced to 5 g twice daily on 1st November 1971 (Fig. 2). On 9th June 1972, when his serum calcium was only 10·6 mg/100 ml and the urinary calcium had dropped to its lowest

Composition of Gewo GT50 A and B

Preparation A

Each ampoule

Calciferol	500,000 I.U.
Aneurine	5·0 mg.
Neostigmine	0.25 mg.
Carbachol	0.08 mg.

Preparation B

Each ampoule

Calciferol	500,000 I.U.
Oestronum	1.0 mg.
Progesterone	5.0 mg.
Neostigmine	0·25 mg.
Carbachol	0·08 mg.

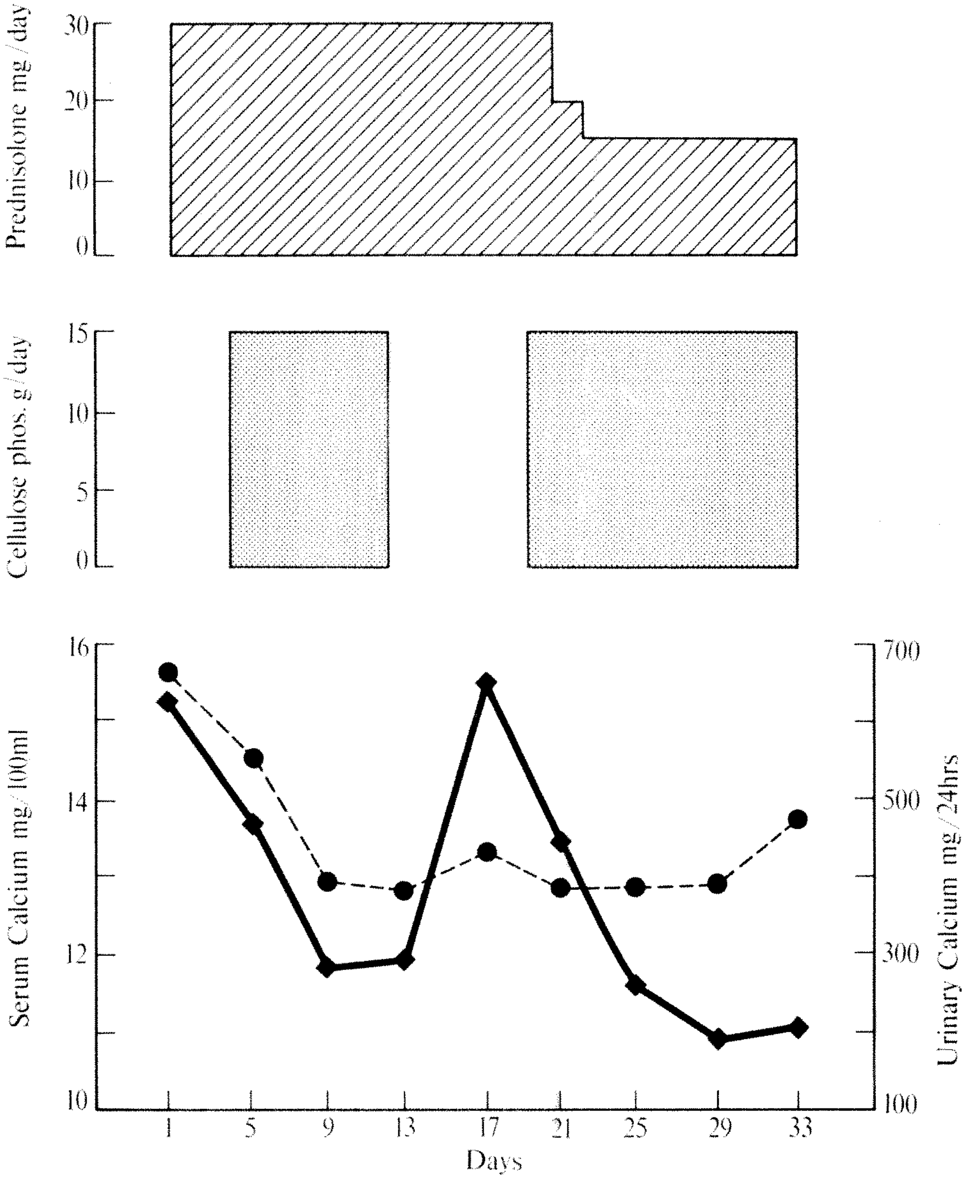

Fig. 1.

level of 70 mg/day, cellulose phosphate was stopped. On 28th September 1972, his serum and urinary calcium levels (10·8 mg/100 ml and 80 mg/day respectively) had remained unchanged and therefore prednisolone was stopped. Following the cessation of treatment his serum and urinary calcium both rose to 11·3 mg/100 ml and 220 mg/day respectively by 25th January 1973. The following results were obtained on 7th January, 1974: Serum creatinine 1·4 mg%, clearance 80 ml/minute, 24-hr calcium excretion 70 mg%, serum calcium 10·2 mg%, serum albumin 4 g%, serum alkaline phosphatase 16 units, blood urea 36 mg%. The patient has had hip replacement of one side, with marked improvement, and is waiting for the other side to be done in the near future (March 1974).

Discussion

Vitamin D intoxication results in hypercalcaemia due to a combination of increased net intestinal absorption of calcium and increased bone resorption (Jackson, 1962, 1967). Hypercalciuria

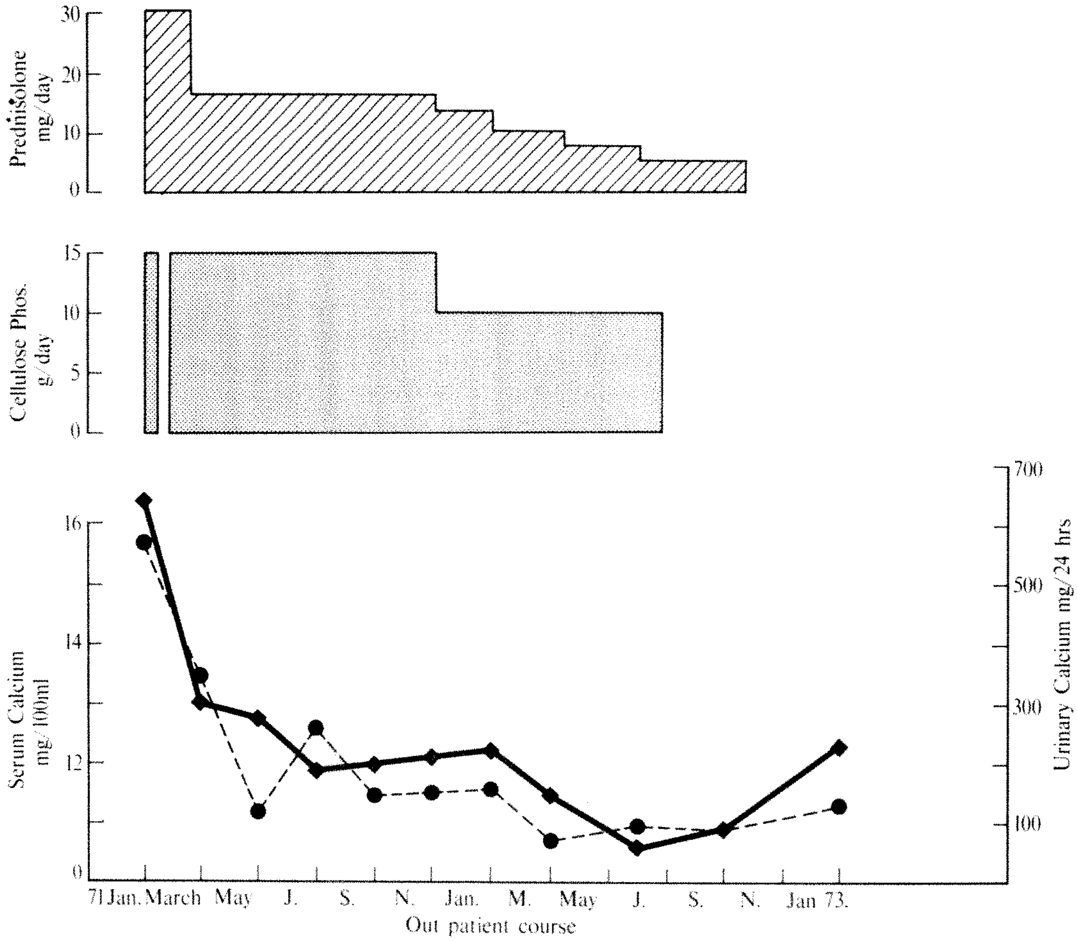

Fig. 2.

results from decreased tubular reabsorption of calcium; it has been reported in the absence of hypercalcaemia and may continue for many months after withdrawing the vitamin (Freedman, 1957). Complications of hypervitaminosis D include calcification in the corneae, pericardium, blood vessels, periarticular tissues, nephrocalcinosis, renal failure, cardiac dysrrhythmias, mental disturbances and coma. In our patient the presence of nausea, vomiting, mental disturbances and decreasing renal function suggested the need for further measures in addition to prednisolone therapy. Dent, Flynn and Nabarro (1953), reported the successful use of cortisone in a patient with hypercalcaemia and renal failure complicating sarcoidosis. Anderson *et al.* (1954), suggested the possibility of an antagonistic action between cortisone and vitamin D accounting for the improvement in their hypercalcaemic patients with sarcoidosis. Successful use of cortisone in vitamin D intoxication due to self administration was reported by Verner, Engel and McPherson (1958).

Cellulose phosphate has been shown to increase faecal calcium excretion and to reduce the urinary calcium content in patients with idiopathic hypercalciuria (Parfitt *et al.*, 1964, Dent-Harper and Parfitt, 1964). Pak *et al.* (1968) reported that 10 g of cellulose phosphate per day orally for 12 days lowered serum calcium concentration significantly in their 2 hypercalcaemic patients. A low calcium diet and withdrawal of the vitamin may take several months to restore the serum calcium to a normal level as vitamin D has a long half life (Howard *et al.*, 1948).

Sodium phosphate appeared contraindicated in our patient in the presence of renal failure as it may induce metastatic calcification (Howard and Meyer, 1948). Ethylene diamine tetra acetic acid can be nephrotoxic (Foreman, Finnegan and Lushbaugh, 1956). We therefore used oral, sodium cellulose phosphate, an ion exchange compound with particular affinity for bivalent ions such as calcium. Lessening of the mental disturbance may occur within 48 hours of starting cortisone (Verner *et al.*, 1958), but the serum calcium usually returns to normal more slowly. Porcine calcitonin (West *et al.*, 1971, Buckle, Gamlen and Pullen, 1972) has been reported to lower the serum calcium promptly and effectively in hypercalcaemia complicating vitamin D intoxication but it is expensive and has to be given repeatedly by injection. The safety and ease of long-term oral administration of cellulose phosphate make this substance a useful addition to existing treatments of hypercalcaemic states.

Summary

A case of hypercalcaemia due to iatrogenic vitamin D intoxication is reported. Following treatment with prednisolone and sodium cellulose phosphate early symptomatic improvement occurred. The 24-hours urinary calcium excretion returned to normal after 5 weeks of treatment but the patient became normocalcaemic only after 13 months. Renal function also improved marginally over this period.

We wish to thank the staff of the biochemistry department, Sefton General Hospital for their help.

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The Surgery and Problems of the Ureter in Human Renal Transplantation

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Guy's Hospital, London and the clinicians of the Renal Units at Guy's Hospital, King's College Hospital, the Royal Sussex County Hospital, Brighton and the Kent and Canterbury Hospital, Canterbury

There is now extensive experimental and clinical experience of renal allotransplantation, but there is still an appreciable incidence of complications referable to disorders of urinary drainage.

The main reported series since 1966 (Table I) shows that the incidence of such urological problems is between 10 and 20% with a significant mortality.

This paper reviews our management of 200 consecutive transplants and describes details of techniques used and developed in the light of our experiences, with particular reference to the problems which arise in relation to the ureter.

Primary Surgical Techniques

Primary urinary drainage was achieved in 196 cases using the technique of uretero-cystostomy. A sub-mucous tunnel was created after the technique of Politano and Leadbetter (1958) and the ureter anastomosed to the mucosa of the bladder after the nipple technique of Paquin (1959) and Starzl *et al.* (1964).

Only a few points need mentioning about these techniques. Paccione (1965) pointed out that the normal ureter, when divided, immediately starts to swell owing to oedema of the adventitia. In the case of the renal allograft this swelling does not start until the kidney is re-vascularised, and the ureter will swell, not only because it has been divided, but also because there is a reactive hyperaemia due to the ischaemia and, possibly, some mild early allograft reaction. Thus the incision through the bladder muscle layer and the sub-mucosal tunnel must be large. We have not attempted to place the ureteric orifice in any particular site in the bladder. We believe that a site convenient for the surgeon is more important than a correct anatomical situation. We have been careful not to disturb the patient's own ureteric orifices. The ureteric epithelium and the vesical mucosa are united by multiple interrupted 4/0 chromic catgut sutures. The ureteric vasculature is not formally ligated, but care is taken to ensure that the interrupted sutures occlude the vessel at the end of the spatulated ureter.

At no time have we found the production of a sub-mucous tunnel difficult and have not found it necessary to use the technique described by Kenefick *et al.* (1972). Only occasionally does haemorrhage within the tunnel occur and we have found that this usually subsides satisfactorily if a little pressure is applied before the ureter is passed along it. Only 2 patients have presented early after transplantation with ureteric obstruction which could possibly have been due to the presence of a sub-mucous tunnel haematoma. A ureteric splint was used in only 3 cases where there was some technical difficulty in performing the ureter-to-mucosa anastomosis. These splints were removed uneventfully on the first postoperative day.

The anterior cystostomy is closed with 2 layers of continuous 2/0 chromic catgut and an outer layer of interrupted catgut. After closure, the intramuscular part of the tunnel is again inspected from the external aspect of the bladder and ascertained to be adequate. Initially, drains to the retropubic space and/or the retro-vesical space were used, but in the last 100 cases drainage has been abandoned as it seemed to serve no useful purpose. Bladder drainage, usually

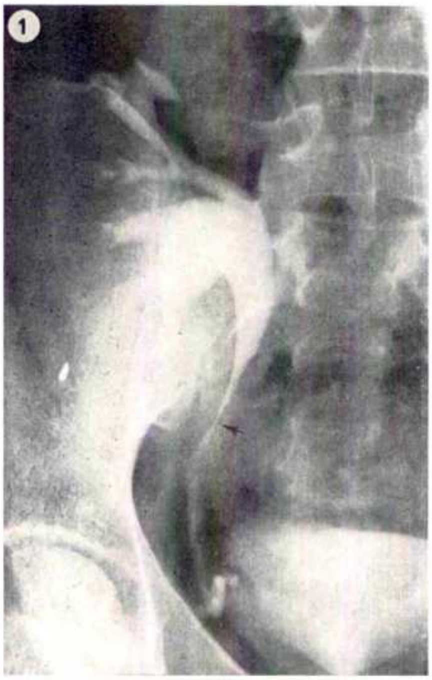
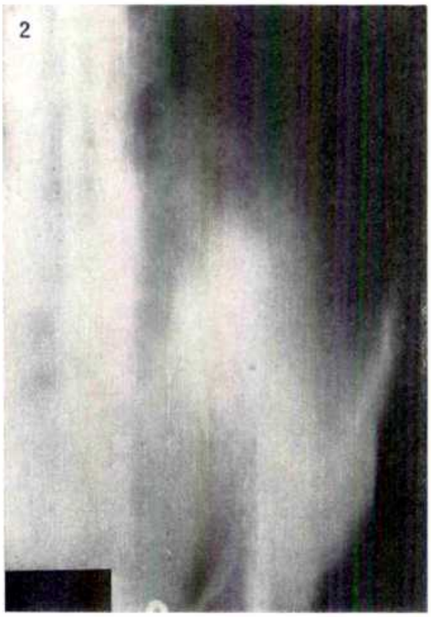


Fig. 1 (C. G.). *Normal findings*. Film taken 5 minutes after injection. There is a good parenchymal thickness with prompt excretion into a normal collecting system and early appearance of contrast in the bladder. The kinking of the ureter proximal to the nipple ureterostomy is a common finding. The ureterostomy itself is frequently visible as a small filling defect in the bladder. A peristaltic contraction is seen in the ureter (arrow).



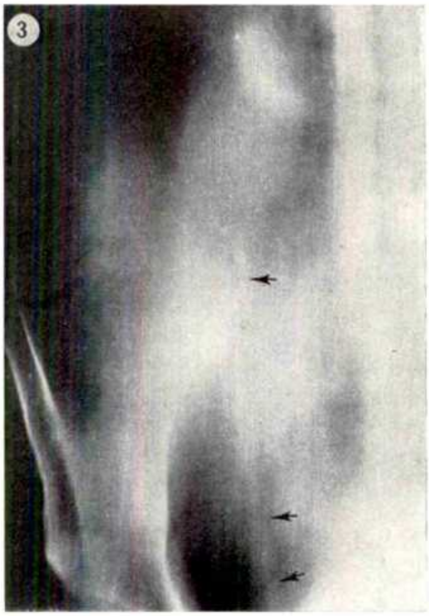


Fig. 2 (J. C.). *Duplex Kidney*. An intravenous urogram of a patient who had an allograft with duplex ureters.

Fig. 3 (G. C.). *Excretion without calyceal opacification*. 14 cm. tomographic cut, 30 minutes after injection of contrast. The renal substance has opacified and the ureter is clearly shown (arrows) with good filling of the bladder. No calyces could be seen on any cuts probably because of compression by the renal substance.

in the form of a Foley catheter, was used in all cases. This was usually removed in 24 to 48 hours if there was anuria, or left in for 7 days if immediate renal function was achieved.

On 2 occasions kidneys with duplex ureters have been provided for transplantation. In both instances they were introduced into the bladder via the same incision and along the same submucous tunnel, but 2 separate nipple ureterostomies were fashioned (Fig. 2). There were no complications. (Ackermann, de Preez and Rösemann, 1971; Barry *et al.*, 1973; Fjeldborg and Kim, 1972*a* and *b*).

Uretero-neocystostomy after the technique of Woodruff *et al.* (1969) and Lissoos *et al.* (1972) was performed on 2 occasions. In each case this was because of a small contracted bladder with a relatively short ureter which made the formation of a tunnel difficult. A splint was used and removed at 14 to 20 days postoperatively after establishment of good renal function. The first healed well, but in the second case the anterior cystostomy used to examine the bladder leaked and had to be closed surgically.

On a further 3 occasions we were presented with kidneys which had ureters which did not extend below the lower pole of the kidney. In these cases a primary uretero-ureteric anastomosis was fashioned. A small anterior cystostomy was made in the bladder and a large (No. F8) ureteric catheter was passed up the ipsilateral recipient ureter. Using this as a guide, this ureter was mobilised 5 or 6 cm above the iliac vessels taking care to maintain the vascular supply along its length. The ureter was divided and the proximal end together with the attached kidney was removed. The distal end was further mobilised until it could be brought into proximity with the donor ureter. The donor ureter was spatulated for 2 to 2·5 cm and the recipient's ureter shortened and then spatulated for a similar distance so that when joined the donor-recipient ureter would lie in an approximately straight line with the bladder. Care was taken to spatulate both ureters along the side away from the ureteric vessels. The ureteric catheter was now inserted into the donor ureter and introduced up to the allograft pelvis. The anastomosis was sutured using multiple interrupted 4/0 chromic catgut sutures. It was then tested for any major leak by instilling a little normal saline along the ureteric catheter. The distal end of the ureteric catheter was now brought out through a separate incision in the bladder wall and through the anterior abdominal wall. The anterior cystostomy was closed in 2 layers as described above and a drain placed down to the ureteric anastomosis. Two cases developed fistulae after removal of the ureteric splint. One healed spontaneously, but the other caused the death of the patient.

Urographic Technique and Findings

In the second week after transplantation, urographic examination of the renal tract is routinely performed whether there is evidence of renal function or not. The way in which urography has been used in the management of these patients is referred to in later sections, but the technique and principal findings are outlined here to show what is done and what can be expected from this investigation.

A plain film and plain tomographic cut are obtained before the contrast is given. These not only confirm that centring and exposure are correct (the usual level of tomographic cut is at the estimated height of the superior pubic ramus) but they also serve as a baseline for any subsequent estimation of the density of the nephrogram. Until it is known that satisfactory renal function has been established—normally some months after transplantation—the standard dose of contrast is 100 ml of sodium iothalamate 70% (Conray 420). In subjects with oedema or heart failure 150 ml of meglumine iothalamate 60% (Conray 280) may be given.

A film is taken at the end of injection to show the initial nephrographic opacification and at about 5 minutes after injection another film is exposed and 3 tomographic cuts are also obtained. The appearances at this stage indicate what further films are needed. Prompt excretion with clear delineation of renal outlines and a normal collecting system (Fig. 1) usually makes further tomography unnecessary. A film at 30 minutes to show the bladder may be followed by an after-micturition film. When concentration of contrast is poor, tomography is essential and more

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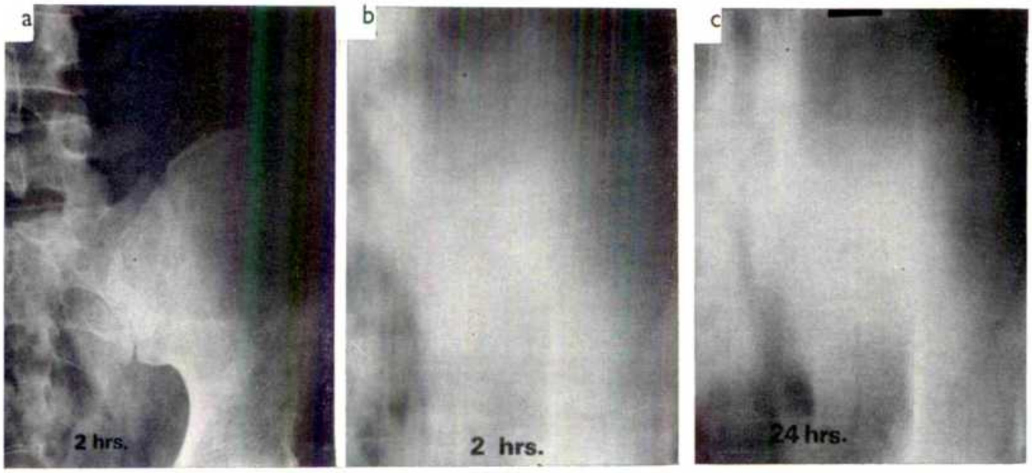


Fig. 4 (K. S.). *Acute tubular necrosis.* (*a*) film and (*b*) tomographic cut, taken 2 hours after injection of contrast. Both show a distinct nephrographic density but this is more obvious on the tomograph. A comparable density was visible on the early films and persisted at 24 hours. (*c*) No calyceal or ureteric opacification occured at any stage.

cuts anteriorly or posteriorly may be required to show the outline of the kidney and the whole of the collecting system. In some cases the calyces and pelvis are not seen, but ureteric and later bladder opacification will show that contrast is being excreted. This is probably due to mild calyceal compression by swollen parenchyma (Fig. 3).

If no opacification of the collecting system occurs delayed films may be required until the diagnosis is clear, *e.g.*, 20 minutes, 1 hour, 4 hours, 12 hours and 24 hours. The value of the pattern of prolonged nephrographic specification without calyceal filling as an indication of tubular necrosis (Fry and Cattell, 1972) is well illustrated by Fig. 4.

In some cases there is no evidence of excretion at any stage, not even a nephrogram. In our material this picture has usually indicated arterial obstruction: we have little experience of urography during rejection because the Rosette Inhibition Test, described by Bewick *et al.* (1972), has made this relatively easy to diagnose without further investigation.

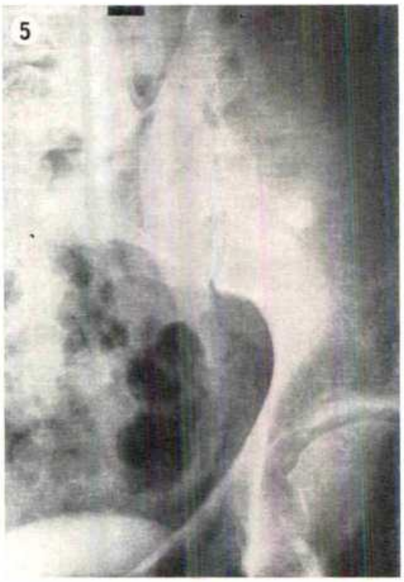
The criteria for the presence of obstruction are similar to those in normally sited kidneys—delayed excretion of contrast with calyceal, pelvic and ureteric distension down to the point of hold-up. In mild obstruction there may be surprisingly little delay in excretion and the main feature is continued distension of the collecting system (Fig. 5).

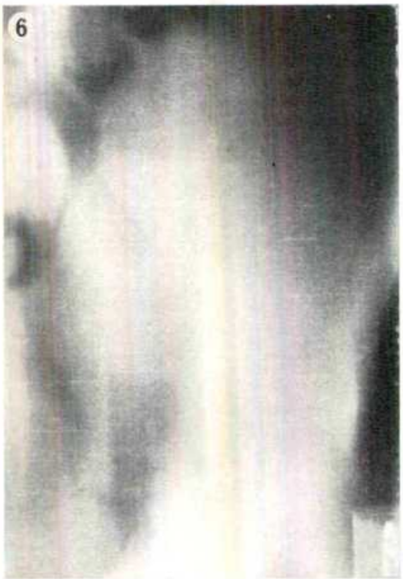
Escape of contrast from sites of anastomosis is easy to identify if the density is adequate, but otherwise may be difficult. However, even when the site of leakage cannot be directly identified it may be possible to make the diagnosis when calyces fill readily but contrast never reaches the bladder (Fig. 6).

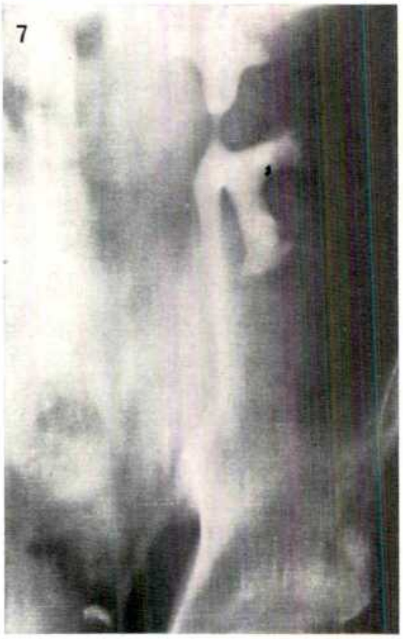
Ureteric Movement after Transplantation

It has already been pointed out that in some patients with obstruction there is relatively little delay in excretion of the contrast and that the main evidence of obstruction is the dilatation of the collecting system and ureter.

In a number of such cases we have considered the alternative possibility that the ureteric dilatation might be due solely to a failure of motor function in the ureter leading to absence of contractions. We know that ureteric contractility is not necessarily impaired by transplantation







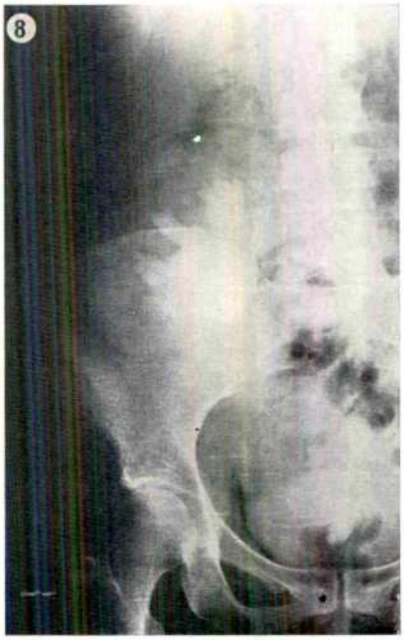


Fig. 5. *Nipple obstruction* (Example 2) (M. R.). Erect film taken after micturition showing persistent distension of calyces and ureters.

Fig. 6. *Leakage from ureter* (Example 12) (C. N.). Good calyceal opacification is seen but no contrast reaches the bladder.

Fig. 7. *Early nipple obstruction* (Example 1) (T. W.). There is slight calyceal and ureteric fullness (a contraction is present in the upper calyceal neck) and minimal delay in the passage of contrast into the bladder.

Fig. 8. *Pelvi-ureteric junction obstruction* due to blood clot in the pelvis (Example 4) (G. R.).

Table I

Overall urological complications in the world literature

			Urological complications		Mortality from urological complications	
Author	Date	Nos. of transplants	Nos.	%	Nos.	%
Leadbetter	1966	25	3	12	1	4·0
Kelly	1967	57	21	38	...	...
Prout	1967	93	9	9·6	2	2·1
Brown	1968	45	14	31	1	2·0
MacKinnon	1968	59	20	33·9	9	15·2
Marshall	1968	58	13	22	...	...
Duke	1969	55	14	25	0	0
Khastagir	1969	123	15	12	2	1·6
Martin	1969	142	24	16	6	4·2
Palmer	1969	37	9	25	3	8·1
Pletka	1969	65	16	25	10	6·5
Salaman	1969	74	11	14·9	2	2·7
Belzer	1970	220	9	4·1	0	0
Williams	1970	158	32	20·2	10	15·8
Starzl	1970	234	23	9·8	5	2·1
O'Donoghue	1971	102	26	25	4	3·9
Powis	1971	20	2	10	0	0
Robson	1971	147	17	11·5	4	2·7
Fjeldborg	1972	180	36	27	12	6·7
Kenefick	1972	46	0	0	0	0
Lissoos	1972	63	3	5	0	0
Wiggishoff	1972	24	8	25	...	...
Paris	1973	42	6	14	0	0

since cine studies which we have undertaken on unobstructed transplants with good renal function have shown normal peristaltic activity in the ureter; contractions in the calyces or ureter may also be seen on some of the still films (Figs. 1 and 7): however, we do not know whether this is always so. Unfortunately those cases with dilated ureters have also shown impairment of concentration and it has not been possible to obtain films of ureteric movement so as to determine whether ureteric atony secondary to transplantation is ever in itself a cause of ureteric dilatation. Our experience so far suggests that the great majority of such cases are in fact due to an anatomical rather than physiological obstruction. If altered contractility is significant it seems more likely that the transplanted ureter is not completely atonic, but is weaker and dilates more easily in response to an obstruction which in the normal ureter could be overcome by peristalsis. To settle this question it would be necessary to undertake pressure studies.

Early Postoperative Function

In those cases in which there was early production of urine and dialysis was not required an intravenous urogram (I.V.U.) was performed 2 to 3 weeks after operation to act as a base line for subsequent examinations and to ensure that there was no ureteric obstruction.

The Early Anuric Kidney

There are 4 causes for anuria at this stage—renal artery or vein thrombosis, ureteric obstruction, rejection, and acute tubular necrosis consequent on the storage of the kidney. The presence of a bruit over the kidney can be useful in establishing if there is blood flow through the allograft, (Braun, 1972 and Anderson *et al.*, 1973). Vascular problems are best shown by the use of an

^{131}I labelled hippuran scan or a renal arteriogram. In our hands the hippuran scan has given consistently good results and we normally perform one on the 2nd or 3rd, and on the 10th postoperative day. If the scan shows no hippuran uptake a renal arteriogram is performed using a percutaneous femoral puncture on the contralateral side, for further evaluation of the kidney. Venography has not been used in our unit except in 2 patients, where there was gross swelling of the ipsilateral leg.

Immunological techniques have been tried with variable success (Bewick *et al.*, 1972; Parker, 1969; Parker and Mowbray, 1971, Posen *et al.*, 1971) in an effort to detect rejection at this time when the clinical and biochemical evidence is scanty. We have found the Rosette Inhibition Test to be extremely useful in confirming our clinical suspicions.

If by the 15th to 20th day the kidney is still severely oliguric a renal biopsy is performed in an effort to gain definitive evidence of the renal histology. If the blood flow is adequate and rejection unlikely, the anuria is probably due to obstruction or tubular necrosis. Fletcher and Lecky (1969), Imray and Gedgaudas (1970) and Williams *et al.* (1970) have shown the value of high dose I.V.U. in assessing the urinary tract particularly in relation to obstruction or leak. Routinely a high dose I.V.U. with tomography is performed on the tenth to fourteenth post operative day. A prolonged nephrogram with faint or absent opacification of the pelvi-calyceal system especially on tomography is suggestive of tubular necrosis rather than obstruction (Fig. 4).

Early Fall Off in Established Renal Function

We define this as a fall off in a previously "life supporting" kidney occurring within 3 months of transplantation. The differential diagnosis lies essentially between rejection and obstruction to the urinary tract. Like Imray and Gedgaudas (1970) we feel that making the diagnosis of rejection by exclusion of obstruction is valuable, and would perform an intravenous urogram before instigating anti-rejection treatment if there was any doubt about the renal tract or if the patients have not had an I.V.U. within the last 2 or 3 months.

The causes of obstruction at this stage are:—

(a) *Poor technique of nipple formation leading to scarring*

Example 1. (T. W.) This patient had a left renal transplant in March 1972. 3 months later an I.V.U. showed some degree of renal tract obstruction with a cut-off in the region of the bladder anastomosis. The ureter and calyces were only minimally distended (Fig. 7). Through a Pfannenstiel incision his bladder was opened and the ureteric anastomosis was found to be stenosed. The sub-mucous tunnel was divided and the mucosa of the bladder sewn to the ureteric epithelium. Thereafter a large bougie passed easily up the ureter to the renal pelvis. Postoperatively the patient had a good diuresis and his renal function improved steadily. A repeat I.V.U. in January 1973 showed minimal obstruction. A percutaneous biopsy at this time perforated the renal pelvis causing heavy haematuria. 24 hours later he became anuric and on exploration the ureter was found to be occluded by intraluminal clot (O'Donoghue, Chisholm and Shackman, 1971). This was removed and the uretero-vesical anastomosis re-fashioned over a No. F12 nasogastric tube. This was brought out through the bladder to the anterior abdominal wall suprapubically, enabling us to irrigate the renal pelvis until the bleeding ceased. It was removed uneventfully at 10 days.

(b) *Obstruction within the sub-mucosal tunnel.* This may be due to ureteric oedema or tunnel haematoma. We have not as yet looked for Papova viruses in such cases (Coleman *et al.*, 1973) but intend to do so in the future.

Example 2. (M. R.). A left renal transplant was performed in July 1972. An I.V.U. 3 weeks later showed some dilatation in the pelvi-calyceal system and ureter which appeared to persist even in the after-micturition film despite the fact that the contrast medium was promptly seen in the bladder (Fig. 5). By January 1973 his renal function had stabilised with a plasma creatinine of 1·3 mg/100 ml but a repeat I.V.U. showed evidence of renal tract obstruction. The sub-mucous tunnel was incised and the obstruction relieved. There was considerable fibrosis around the ureter in the tunnel, but the ureter itself appeared macroscopically normal.

(c) *Ischaemia of the ureter*

Example 3. (E. K.). This patient received a kidney in June 1971 which functioned immediately, but 24 hours later the urine volume slowly decreased and an I.V.U. showed some evidence of obstruction. The nipple was found to

Table II

Urological complications due to primary obstruction in our series

Name	Date of Transplant	Time of Presentation post Transplant	Cause	Treatment	Outcome	Comment
T.Q. (Example 5)	5.12.68	9 months	chronic ureteric rejection	Anastomosed renal pelvis to bladder	Reflux without bacteriuria. Maintaining renal function	—
S.M. (Example 11)	7.7.70	3 days	nipple technique	Reanastomosed ureter × 3 with recurrent fistulae. Ileal conduit from renal pelvis to bladder	Satisfactory urinary drainage. Died sepsis at 9 months	Ureteric splint used
E.K.	30.6.71	5 days	nipple necrosis	Reanastomosed ureter	Recurrent fistula leading to sepsis and death	Ureteric splint used
D.D. (Example 6)	27.7.71	9 months	lymphocoele	Internal and external drainage	Improved renal function but died 14 days later of chest infection	—
C.A.	30.10.71	4 days	nipple necrosis	Reanastomosed ureter	Died of respiratory arrest postoperatively	Ureteric splint used
F.L.	11.12.71	2 days	nipple technique	Reanastomosed ureter	Recurrent fistula leading to sepsis and death	No splint
L.H.	9.3.72	2 days	nipple	Reanastomosed ureter	No fistula. Good function at 1 year	Large silastic splint
T.W. (Example 1)	21.3.72	3 months	nipple technique	Reanastomosed ureter	Mild recurrent stenosis at 9 months. Clot obstruction following biopsy-reanastomosis No recurrence. No fistula	Nasogastric tube splint
M.R. (Example 2)	6.7.72	10 days	submucosal haematoma	Incision of tunnel	Complete resolution	—
G.R. (Example 4)	19.3.73	10 days	intra pelvic haematoma	evacuation and nephrostomy	Re-exploration and trans-ureteric nasogastric tube-healed	Nasogastric tube instead of nephrostomy

be necrotic. The ureter was reanastomosed to the bladder with some difficulty. A ureteric catheter was inserted. 5 days later good renal function was established and the ureteric catheter was removed 2 weeks later.

(d) *Clot obstruction of the renal pelvis*

Example 4. (G. R.). This patient received a kidney in March 1973 which functioned immediately. Ten days later an I.V.U. showed an obstruction at the pelvi-ureteric junction (Fig. 8). Exploration revealed a quantity of clot in the renal pelvis. Histology did not reveal a papilla. The clot was removed and a nephrostomy was performed, but as this failed to heal, the ureter was re-explored 3 weeks later and a No. 10 FG nasogastric tube passed from the bladder up the ureter to the pelvis. Omentum was placed around the nephrostomy wound. Eventually all tubes were removed with satisfactory urinary drainage.

(e) *Early lymphocoele.* Innocencio *et al.* (1969) and Schweizer *et al.* (1972) reported several cases. They postulated that a lymphocoele developing at this time was due to poor surgical technique in failing to ensure that the lymphatics were effectively ligated around the iliac vessels at the time of operation. We have had no recognised cases of this condition in the early phase.

(f) *Ureteric kinking.* Belzer *et al.* (1970) and Salaman *et al.* (1969) each reported 3 cases where kinking of the ureter due to technical difficulties produced anuria. We have had no similar cases.

(g) *Abscess Formation.* Fletcher and Lecky (1969) and Zazgornik *et al.* (1973) described cases in which a perinephric abscess appeared to cause kinking of the ureter. Drainage of the abscess resulted in relief of the obstruction. Although we have had several small abscesses involving the ureter, especially at its site of insertion in the bladder, we have had no cases where we were able to demonstrate obstruction due to the abscess.

Late Fall Off in Established Renal Function

This is defined as a fall off in renal function occurring after 3 months of satisfactory function. It is due to progressive scarring, rejection of the ureter, the formation of a late lymphocoele (Innocencio *et al.*, 1969; Madura, Dunbar and Cerilli, 1970; Schweizer *et al.*, 1972) and possible papillary necrosis (Edmondson *et al.*, 1972).

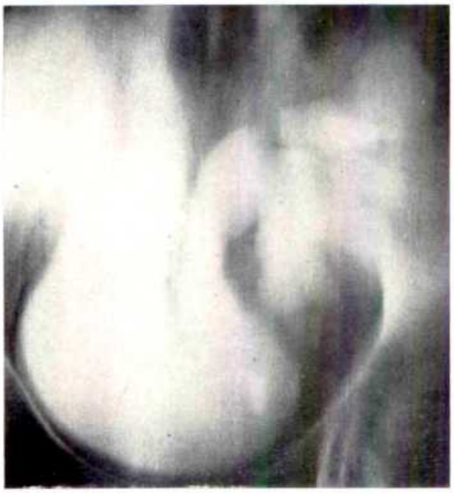
Acute rejection episodes are frequently managed with therapy that includes external radiation. There is a theoretical possibility that radiation strictures of the ureter may result, but we have had no indications that such a complication has occurred in our series.

Example 5. (T. Q.). In December 1969 this patient had a left renal transplant, but 6 months later an I.V.U. showed gross distension of the calyces and ureter (Fig 9). A micturating cystogram showed reflux up the left residual ureteric stump, but no reflux up the transplant ureter. A small diverticulum was noted on the right. The transplant was explored. Diverticulectomy was performed and the left ureteric stump was removed. There was great difficulty identifying the transplant ureter, but when isolated it was found to be almost completely obliterated from the renal pelvis to the bladder. A direct renal pelvis to bladder anastomosis was performed. Since then there has been no evidence of bacteriuria nor deterioration in the renal function. The patient has been told to "double micturate" but says that he never passes any urine at the second attempt. Histology of the ureter showed evidence of long-standing rejection.

Example 6. (D. D.). This patient had a right renal transplant in June 1971. The allograft had 2 ureters which were inserted through a single vesical and sub-mucous tunnel, but a double nipple ureterostomy was performed. At 9 months he presented with a fluctuant swelling around his kidney. An I.V.U. showed a mass behind the allograft obstructing the ureter. The bladder was markedly displaced to the right (Fig. 10). At exploration he had a large lymphocoele containing 1500 ml of slightly turbid fluid. The ureters were seen to be distended and on releasing the fluid they collapsed. His bladder was opened and a probe passed easily up both ureters. The cyst was internally marsupialised and the wound closed with drainage. Postoperatively there was very little external drainage and an I.V.U. showed that there was no obstruction.

Complications of Ureteric Obstruction

Table II shows the complications due to primary ureteric obstruction in our series. The treatment and outcome are presented. In our experience early diagnosis and operative intervention is



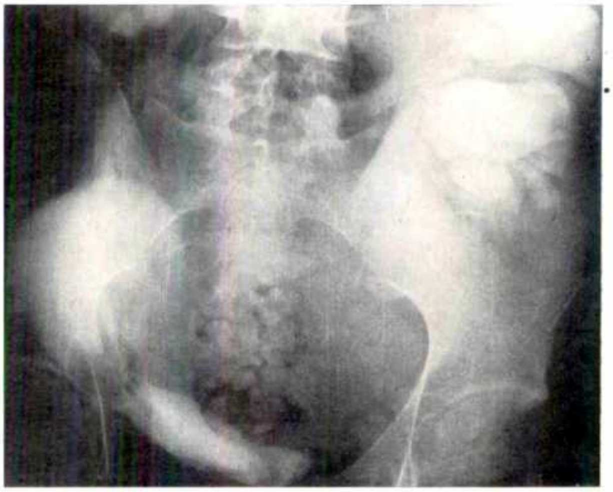


Fig. 9. *Severe obstruction* (Example 5) (T. Q.). A short ureter is present with marked obstruction producing severe dilatation.

Fig. 10. *Obstruction of duplex kidney by lymphocoele* (Example 6) (D. D.). There is severe distension of the calyces of both moieties and the bladder is markedly displaced to the right by a pelvic mass. An indwelling catheter lies in the bladder. After operative removal the kidney returned to normal.

imperative, but a high incidence of fistula formation occurs unless adequate ureteric drainage is achieved. The largest ureteric splints do not seem to drain well and often get blocked. More recently we have used a soft FG8 or FG10 nasogastric tube to splint the ureter. This lies snugly in the ureter, has multiple perforations and has a radio-opaque tip which can be easily visualised on a plain X-ray film to ascertain its position. With this type of splint no secondary fistula has occurred.

A formal nephrostomy tube as drainage has been considered in managing the obstructed ureter or in cases of primary ureteric fistulae, but this involves mobilising the kidney and possibly spreading any local sepsis. It is not an easy technique to use in an oedematous kidney especially without opening the renal pelvis and for these reasons has never been used.

Urinary Fistulae

"The urinary fistula is an exceedingly grave complication in a patient with a renal transplant, since immunosuppressive drugs impair the defences against infection and a septic fistulous tract is likely to follow" (*British Medical Journal*, 1966). Table III shows the incidence of urinary fistula and its mortality in the published series. From these figures it would seem that a urinary fistula with the possible exception of those fistulae which can be treated by a simple urethral catheterisation (*i.e.*, leaks from the anterior cystotomy, and possibly leaks from around the ureteric implantation) should be treated by early transplant nephrectomy in an effort to save the patient's life.

The diagnosis soon after operation may be quickly apparent as an external leak if drains are used, but if drains are not used or have been removed already, the first signs are usually malaise, pyrexia, pelvic fullness, tenderness and oliguria. We have found that in addition to confirming the clinical suspicion of a leak the I.V.U. also indicated its site. Cystography can also be helpful.

The causes of urinary fistulae are:—

(a) *Inadequate closure of the anterior cystotomy*

Example 7. (D. G.). In August 1972 this patient received a left renal transplant which functioned 12 days later. 5 days later he complained of a sudden onset of severe suprapubic pain and his 24 hour urine volume had fallen off.

Table III

Incidence of urological fistulae formation and outcome in the world literature

			Fistulae		Mortality due to fistulae	
Author	Date	Nos. of Transplants	Nos.	%	Nos.	%
Prout	1967	93	7	7·5	2	2·0
Salaman	1967	70	7	10·0	2	3·0
Walsh	1969	31	3	9·8	3	9·8
Palmer	1969	36	6	16·6	3	8·4
Martin	1969	142	17	11·9	6	4·2
Williams	1970	158	27	17·0	9	5·6
Belzer	1970	220	4	1·8	0	0
Starzl	1970	234	9	3·8	3	1·2
Rees	1972	Not stated	9	...	5	...
O'Donoghue	1973	130	15	12·0	2	1·5

The pain was relieved by urethral catheterisation and a cystogram showed a leak from the anterior cystotomy. This patient had been known to have a small contracted bladder and at operation it was thickened and trabeculated. A urethral catheter was left in situ for 3 months. A cystogram 1 month later showed he still had evidence of leakage when more than 150 ml of contrast were in the bladder. At 3 months the urethral catheter was removed with no recurrence of the leak.

Example 8. (T. B.). In May 1970 this patient had a left renal transplant, but it was explored 10 days later for anuria A dilated ureter was reanastomosed to the bladder whereupon good renal function was established. Soon after this he developed a urinary fistula, which closed spontaneously after urethral catheterisation. 2 months later a cystogram showed no evidence of leak and the urethral catheter was removed.

(b) *Ureteric ischaemia with early fistula formation*

Example 9. (J. T.). This patient had a right renal transplant in December 1972 from his father. 4 days later there were signs of a urinary leak. On exploration the ureteric vein was distended and thrombosed. The ureter was necrotic. Exploration of the hilum of the kidney revealed a ligature on a tributary of the main renal vein which seemed to be partially occluding the ureteric branch. A Boari flap was fashioned and anastomosed to the renal pelvis splinted by a No. F12 nasogastric tube. Satisfactory renal function resumed and the splint was removed at 4 weeks.

Example 10. (J. B.). In March 1970 this patient received a right renal transplant. The kidney was from a 4 year-old child. The vascular anastomoses were uncomplicated and the ureter looked well vascularised as it was inserted into the bladder. 6 days later a urinary fistula developed and an I.V.U. showed leakage from around the ureter. Exploration of the kidney showed a discrete necrotic hole in the pelvis of the kidney. This was oversewn and omentum stitched around (MacKinnon *et al.*, 1968 and O'Donoghue *et al.*, 1971). 24 hours later the fistula recurred. On re-exploration the right recipient ureter which had been left in situ following his pre-transplant bilateral nephrectomy was mobilised. The cranial end was spatulated and sewn over the perforation. The bladder was opened and a large ureteric splint inserted along the recipient ureter into the pelvis of the allograft. 1 month later the external fistula had completely healed and a retrograde pyelogram along the in-dwelling splint showed no extravasation of contrast. The splint was removed uneventfully.

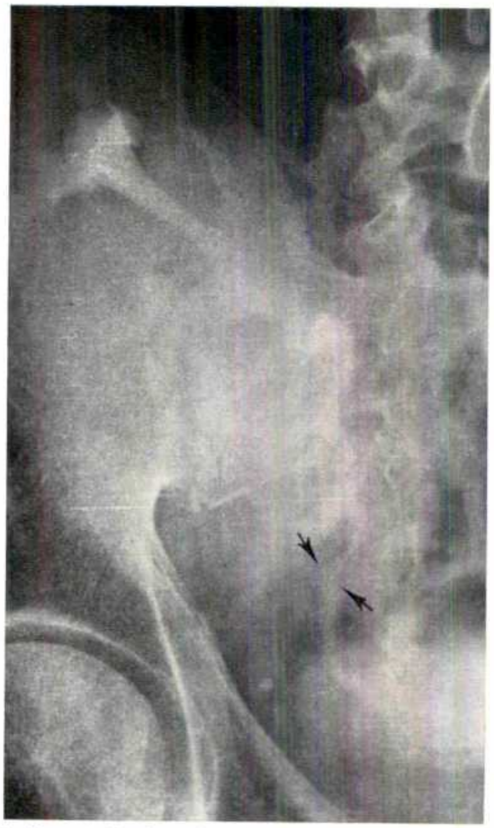
The patient has continued in excellent health since then and repeated urograms have shown that the transplanted ureter is probably occluded with the urine draining down the recipient ureter (Fig. 11).

Example 11. (S. M.). This patient received a kidney from her cousin in September 1969. 13 days later the kidney was re-explored for failure to function and a large haematoma was evacuated. The anterior cystotomy wound was re-opened and there appeared to be some evidence of ureteric obstruction. This was repaired, but after withdrawal of the ureteric catheter a persistent urinary leak occurred. 12 days later she was treated for an acute rejection episode and in October 1969 she had a direct repair of the leak from the lower end of the ureter by re-anastomosing the ureter to the bladder and covering it with an omental graft. The fistula failed to close and two further attempts were made to reimplant the ureter. The leak persisted and in January 1970 the whole ureter was replaced by an ileal

Table IV

Urological complications due to primary fistula formation in our series

Name	Date of transplant	Time of presentation post transplant	Cause	Treatment	Outcome	Comment
T.B. (Example 8)	19.5.70	30 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	—
E.W.	17.6.71	10 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	—
L.B.	9.7.71	2 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	—
D.D.	10.1.72	14 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	—
D.G. (Example 7)	22.8.72	5 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	Small contracted bladder
P.B.	23.8.72	10 days	Ant. cystostomy leakage	Bladder drainage	Healed spontaneously	—
B.J.	1.12.72	3 weeks	Ant. cystostomy leakage	Bladder drainage for 3 months without resolution. Exploration and closure	Healed	Narrow neck between bladder and ureterovesical space
E.F.	28.1.73	5 days	Ant. cystostomy leakage	Bladder drainage for 3 months without resolution. Exploration and closure	Healed	Very small contracted bladder
J.B. (Example 10)	13.3.70	6 days	Renal pelvis necrosis	Oversewn with omentum. Fistula recurred. Sutured ipsilateral recipient ureter over fistula with ureteric splintage	Healed	Inadequate splintage
S.D.	27.2.72	14 days	Ureteroureteric anastomosis with splintage		Healed	—
E.H.	26.4.72	5 days	Ureteroureteric anastomosis with splintage	Splint removed too soon. Recurrent fistula which failed to close with further splintage	Died of sepsis	Inadequate primary splintage
C.N. (Example 12)	28.7.72	19 days	Ureteric rejction	Reanastomosed twice	Persistent fistula Died of sepsis	Inadequate splintage
D.B.	13.11.72	7 days	Ureteric necrosis	Reanastomosed. No fistula	Died. Chest infection	—
J.T. (Example 9)	21.11.72	4 days	Ureteric venous thrombosis	Excised ureter and anastomosed renal pelvis to Boari flap	No fistula. Healed well	—



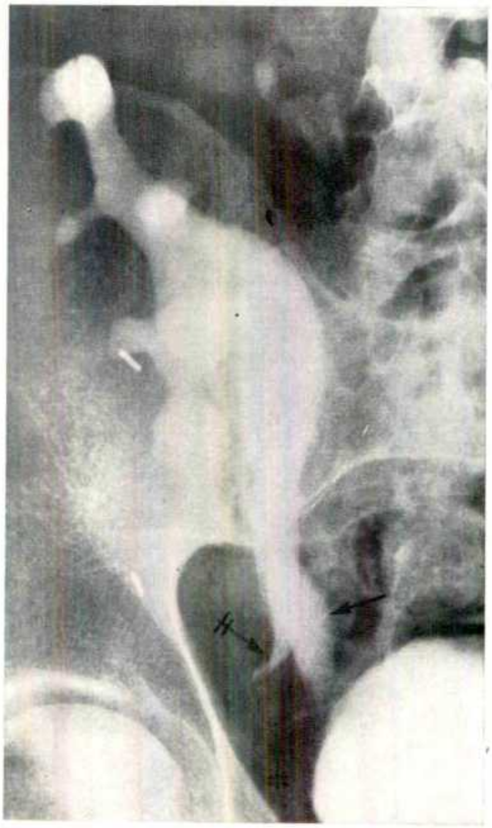


Fig. 11. *Ureteric Fistula with recovery* (Example 10) (J. B.). Urogram showing irregularity of upper ureter and a "diverticulum" just below where it is anastomosed to the recipient ureter (arrows). This is due to partial filling of the necrosed lower ureter.

Fig. 12. *Reflux* along transplanted and recipient's own residual ureters (J. M.).

conduit from the pelvis of the kidney to the bladder. After initial leakage the area healed satisfactorily. An I.V.U. and cystogram 3 months later showed that there was some reflux up the ileal conduit, but no evidence of obstruction and the patient recovered good renal function.

Example 12. (C. N.). This patient received a left renal transplant in July 1972. 19 days later the kidney had still not functioned and an I.V.U. showed that contrast was excreted into a normal pelvi-calyceal system. There was no evidence of obstruction. Unfortunately it was not appreciated that with this amount of dye in a normal pelvi-calyceal system there should have been some dye in the bladder (Fig. 6). Two days later he developed a tenderness around the kidney and inguinal region with some oedema over the same area. Exploration of the kidney showed extensive urinary leakage. There was a small perforation in the ureter at the back of the bladder and histology showed acute rejection of the ureter although there seemed to be histologically and immunologically no rejection within the kidney. The ureter was re-anastomosed with some difficulty to the anterior surface of the bladder over a large ureteric splint. 14 days later the ureteric catheter was removed with immediate recurrence of his urinary fistula. 4 days later the patient died of sepsis. The kidney showed no evidence of rejection, but there was evidence of marked tubular necrosis.

(c) *Segmental infarction in the transplanted kidney*. Cases have been reported by Fox and Tottenham (1972) and O'Donoghue, Chisholm and Shackman (1973). The leak was successfully repaired and the patient survived. We have no similar experience.

Table IV shows our complications due to primary urinary fistulae. Those of the bladder were all confirmed by cystogram. Urethral catheterisation allowed each to heal spontaneously and the signs of leakage resolved in 24 to 48 hours in all but 2 cases. Exploration of the bladder was performed in these 2 cases followed by healing.

Of the ureteric leaks only 2 died with recurrent leaks and sepsis. We believe that both of these could have been prevented by improved urinary drainage—as could those cases of recurrent fistulae which eventually healed spontaneously. A nasogastric tube is now used and seems more successful. Adequate drainage seems essential to prevent the infective complications of recurrent fistula.

Vesico-ureteric Reflux

We do not perform cystograms as a routine on our patients. Uranga *et al.* (1972) noted 10 cases of reflux in 239 transplants, but in all cases this was confined to the recipient's own ureters and it is of note that all these patients had a bilateral nephrectomy prior to the transplant operation. They noted no reflux in the transplanted ureter and felt that the recipient nephrectomy may have initiated some defect of ureteric peristalsis or else the normal function of the uretero-vesical junction was impaired by putting the new ureter too close to it. Powis, Barnes and Dawson-Edwards in a series of 20 transplants noted reflux in 50% of the transplanted ureters and 25% of the patient's own ureters.

Example 13. (J. M.). This patient, after bilateral nephrectomy for hypertension, had a transplant in March 1969 which did not function satisfactorily for 81 days. His function improved steadily, but an I.V.U. in July 1970 showed some dilatation of the calyces in the transplant. There was also reflux up the transplant ureter and both the original ureters (Fig. 12). He has never had bacteriuria and has maintained his renal function satisfactorily to the present day.

Renal Inversion

Leadbetter, Monaco and Russell (1966) mentioned that several cases have been reported without ill effects. We have had 2 of these cases.

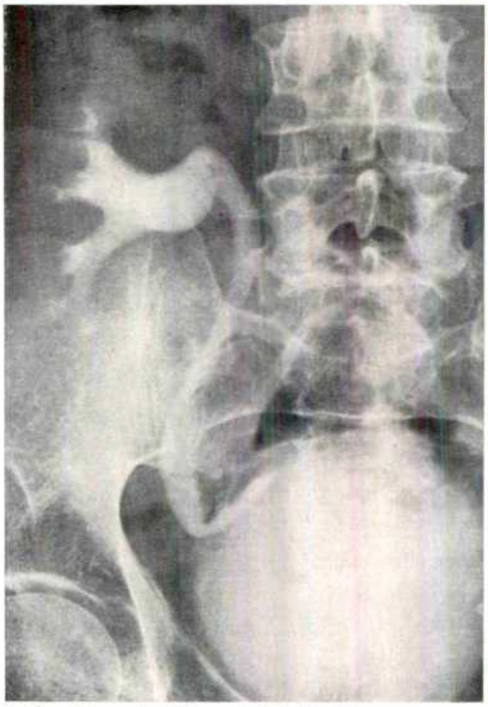
Example 14. (H. B.). In July 1972 this patient had what appeared at operation to be a perfectly routine right renal transplant. 3 weeks later he had a routine I.V.U. which suggested that the kidney had been put in upside down. He has a good renal function with a plasma creatinine of 1·2 mg/100 ml and seems to be draining urine well with no evidence of obstruction (Fig. 13).

Example 15. (M. S.). This patient received a right cadaver transplant into the right iliac fossa in December 1972. After the vascular anastomoses were completed, it was found to be inverted. As it had a long ureter this was anastomosed to the bladder in the routine manner. Although the transplant functioned the plasma creatinine never fell below 2·0 mg/100 ml and an I.V.U. in January 1973 showed a hydronephrosis with a normal ureter (Fig. 14). Before exploration could be attempted her function deteriorated and she died suddenly of hyperkalaemia. At postmortem she had a large hydro-pyonephrosis with evidence of pelvi-ureteric obstruction, but this did not appear to be at the site where the ureter was bent over. There was also evidence of pyelonephritis in the partner allograft.

For this "technical anomaly" to occur 3 factors seem to be important. Normally we have inserted the allograft into the contralateral iliac fossa wherever possible. In these circumstances the renal vein is lateral to the artery. If the donor surgeon fails to identify and label the kidneys correctly, the transplant surgeon may inadvertently open the ipsilateral iliac fossa. Then, especially if the ureter is long, he can position the kidney with the vein on the lateral side and the ureter still appears to be pointing to the bladder. This kidney is, of course, inverted.

Calculus Formation

Starzl *et al.* (1970) have reported 2 cases, but we have no experience of this complication. 2 of our patients had chronic renal failure secondary to oxalosis. Both developed deposits of oxalate in their transplanted kidneys within 3 months and died shortly after of transplant failure due to oxalosis.



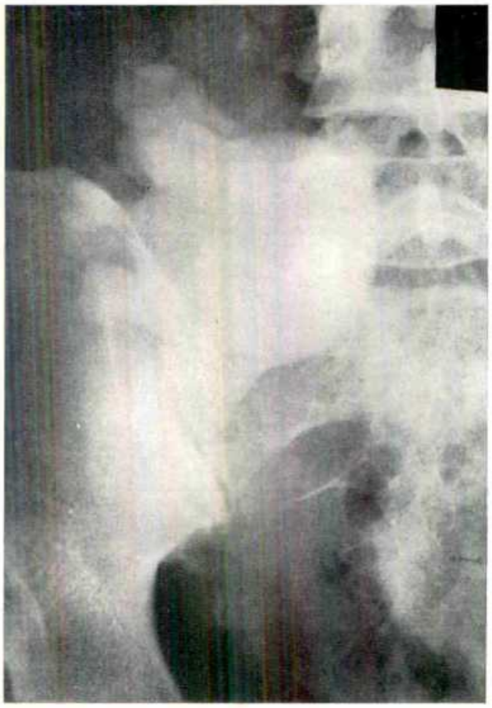


Fig. 13. *Renal inversion* (Example 14) (H. B.).

Fig. 14. *Hydronephrosis due to pelvi-ureteric junction obstruction* in an inverted kidney (Example 15) (M. S.).

Discussion

Table V summarises our urological complications following 200 consecutive renal transplants. In our series as in all others a urinary fistula (whether primary or secondary) was still responsible for a considerable mortality. This we think can be reduced by more effective urinary tract drainage.

Prevention, though, is better than cure—care to ensure adequate ureteric vasculature is essential.

When removing kidneys from a donor the hilum of the kidney should be dissected as little as possible in an effort to avoid damage to the ureteric vessels. Lower pole arteries should be utilised as these may carry the ureteric artery. If they have been cut then they can be anastomosed to the main renal artery end-to-side before the kidney is revascularised, or end-to-end to the inferior epigastric artery after revascularisation of the rest of the kidney.

Care must be taken with the nipple ureterostomy, and once anastomosed it should be checked for adequate patency before bladder closure. If a ureteroneocystostomy is used this can be done before the last 2 or 3 sutures are inserted.

Renal inversion should never occur, but is not necessarily a major catastrophe if it does.

Summary

This study describes the urological complications associated with 200 consecutive renal allotransplantations performed between May 1967 and March 1973. Of these 176 were cadaver kidneys and 24 kidneys were from live donors.

Table V

Overall urological complications in our series

Cause	Incidence		Nos. of kidneys removed for urological reasons	Patient mortality due primarily to urological complications	
	Nos.	%		Nos.	%
Primary obstruction	10	5·0	0	4	2
Primary fistulae: ureter	6	3	0	3	1·5
Primary fistulae: bladder	8	4	0	0	0
Vesico-ureteric reflux	1	0·5	0	0	0
Renal inversion	2	1	0	1	0·5
Calculus formation	0	0	0	0	0
Total	27	13·5	0	8	4

An outline of the surgical technique is followed by details of the postoperative management in straight-forward and complicated cases. Details of radiological techniques are discussed.

Urological complications are divided into those occurring soon after surgery and those developing after 3 months of satisfactory function. The possible causes are listed and means of identifying them described. The outcome of the various complications is described.

There was an overall incidence of urological complications of 13·5% (5% due to primary obstruction and 7% due to primary fistula formation). The mortality directly due to a urological complication was 4% and was highest (2%) in those due to primary urinary obstruction.

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Further Experience with the Rectosigmoid Bladder

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Our preliminary experience with rectal bladder for diversion of urine has previously been published (Ghoneim and Safwat 1968; Ghoneim, 1970). The aim of this paper is to present the results of a larger series, followed up for a longer period.

Patients and Procedures

Between 1968 and 1972 the rectal bladder with a terminal colostomy was employed as a method of urinary diversion in 89 patients. The age and sex distribution are given in Table I.

Table I

Age and Sex Distribution

Age	20-29	30-39	40-49	50-59	60	Total
Males	3	16	25	18	5	67
Females	2	9	7	4	—	22
Total	5	25	32	22	5	89

Carcinoma of the bladder was the indication for operation in all cases. Cystectomy and diversion were done at the same sitting in all but 2 cases. In these 2 cases cystectomy and bilateral cutaneous ureterostomy were performed as a first stage, followed by the construction of a rectal bladder 3 months later.

Table II

Period in Years	No. of Cases
less than 1	10
1-2	12
2-3	20
3+	18
Untraced	4
	64

12 patients died in hospital.
13 developed recurrences and died during follow up.

The patients were regularly assessed postoperatively, the longest follow-up available at present being 3 years (Table II).

Technical Aspects

The bowel should be divided at least 12·5 cm above the rectosigmoid junction thus increasing the capacity of the reservoir.

In our view the best technique is a direct end-to-side mucosa-to-mucosa anastomosis to avoid the subsequent development of a stricture at the anastomotic site. This can best be achieved using Goodwin's technique for uretero-colic anastomosis (Goodwin *et al.*, 1953). The upper end of the rectosigmoid pouch is closed. The anterior wall of the rectum is incised for 3 cm between 2 stay sutures (Fig. 1). A button of tissue is then excised from the side wall of the rectum. The ureter is withdrawn through the opening taking care to avoid kinking or twisting. A mucosa-to-mucosa anastomosis is carried out from within the rectal lumen. This is reinforced with a few interrupted sutures between the serosa of the rectum and adventitia of the ureter. A self-retaining catheter is inserted in the rectum and kept indwelling for 10 days.

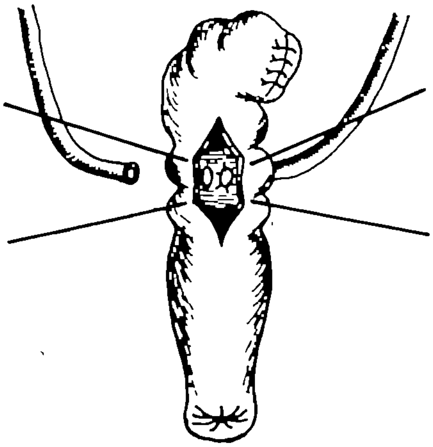

Fig. 1. The uretero-rectal anastomosis.

Table III

Postoperative Mortality

Peritonitis, adhesive ileus	5
Septic shock	3
Renal failure	2
Coronary thrombosis	1
Pulmonary embolism	1
	12 = 13·5%

Results

Postoperative Mortality

12 patients died in hospital following operation giving a postoperative mortality rate of 13·5%. The causes of the postoperative deaths are outlined in Table III, more than half of the fatalities being due to septic complications.

Postoperative Morbidity

Convalescence was uneventful in 55 patients; 22 developed serious complications (Table IV). Sepsis and urinary leakage were common. The rectal tube was retained in situ until leakage ceased, and if still present at 4 weeks the condition was arbitrarily defined as a fistula. This occurred in 4 patients, each of whom was re-explored and in all instances the lower end of the ureter was found to have sloughed.

Table IV

Morbidity: Postoperative
Complications in 22 Patients

Pelvic collections	3
Wound sepsis	9
Leakage of urine	9
Burst abdomen	3
Intestinal obstruction	5
Chest infection	6

Radiological Studies

The function and configuration of the upper urinary tract were assessed by intravenous pyelography. The fate of 115 kidneys thus examined is shown in Table V.

Table V

Radiological Appearance of
115 Kidneys Following Operation

Unchanged	57
Improved	31
Deteriorated	27

The pyelographic appearance was unchanged in most cases (Fig 2). Evidence of improved drainage of the upper urinary tract could be demonstrated in 27% of cases.

Deterioration in the radiological appearance was seen in 27 kidneys (Table VI). Anastomotic strictures were the commonest cause of deterioration (Fig. 3). Pyelonephritis (Fig. 4) was observed in 9 kidneys. Ureteral kinks (Fig. 5) responsible for back pressure, were seen on 3 occasions.

Contrary to what might be expected, reflux does not seem to be a factor of major importance in renal deterioration. All cases studied by ascending proctography revealed free procto-ureteral reflux (Fig. 6, A). It seems that the deleterious effects of reflux are minimal in a low pressure system, such as that which exists in the rectal bladder (Smith and Hinman, 1955; Ghoneim, 1970).

Rectal Bladder Function

The rectal bladder proved to be a balanced reservoir. Proctography and post-evacuation films (Fig. 6), showed that the rectal bladder can empty completely. This was a constant finding supported by the evidence of rectal catheterisation.

Table VII indicates the frequency of voiding in 60 patients. It is of interest that the anatomical (measured volumes) capacity is greater than the ultimate functional capacity (voided volumes); an observation reported also by previous investigators (Maluf, 1958; Stamey, 1971). Measurements obtained in 12 cases are given in Table VIII.

Consideration of the physiology of the rectum provides a possible explanation for this observation. Distension of the rectum is the stimulus normally interpreted by individuals as a desire to pass faeces. The lower part of the rectum immediately above the anal sphincter is more sensitive to this latter form of stimulation than is the upper part (Goligher and Hughes, 1951). In this study the anatomical capacity was measured while the patients were supine, but the functional capacity was measured while the patients were erect. In the latter case urine collecting in the reservoir was readily accumulated in the lower rectum, stimulating an early desire to void. This was demonstrated radiologically in 6 patients (Fig. 7). Ascending proctograms were carried out in erect and supine positions. 50 ml increments of diluted urographin were slowly introduced into the rectum via a catheter and serial radiographs were taken. With the patient lying supine, the upper rectum and sigmoid loop began to fill (S1). As the volume increased, the contrast medium refluxed into

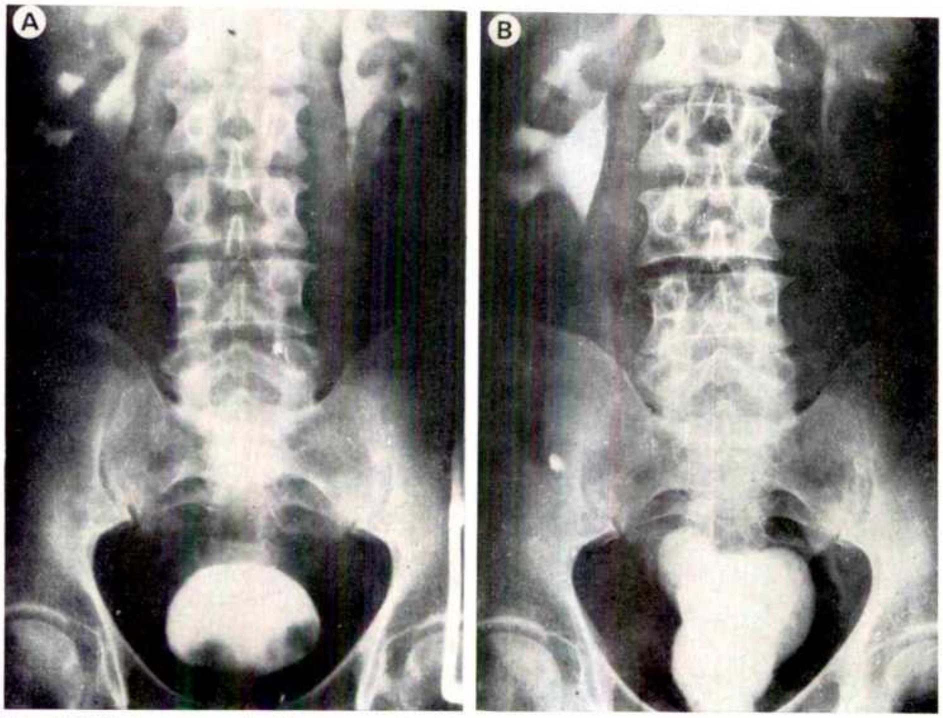

Fig. 2. I.V.P. A, preoperative, B, postoperative. Demonstrates unchanged appearance.

Table VI

Causes of Deterioration of Radiological Appearance

Stricture	15
Kinks	3
Pyelonephritis	9
	27

the ureters and kidneys, and finally the lower rectum became distended (S6), when the patient felt the desire to void. In contrast, proctograms performed in the erect position showed filling of the lower rectum at an earlier stage (E1), leading to an early onset of the desire to void (E4).

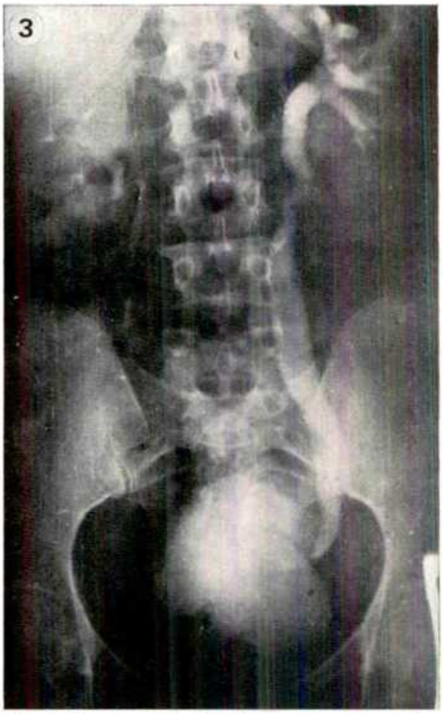

Fig. 3. Postoperative I.V.P., a stricture on the left uretero-rectal anastomosis

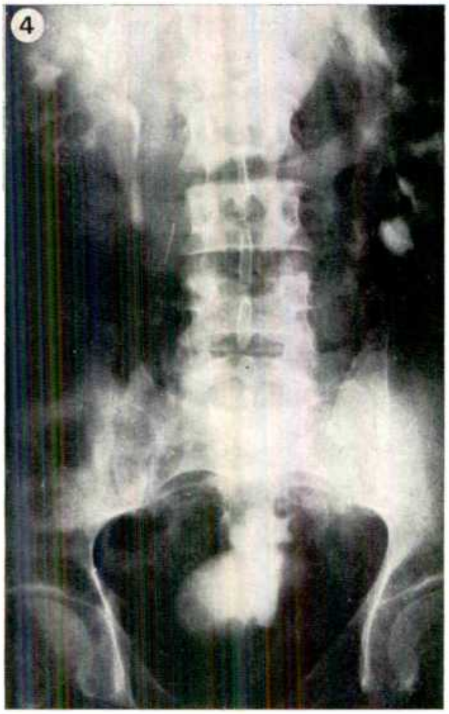

Fig. 4. I.V.P., Left pyelonephritis.

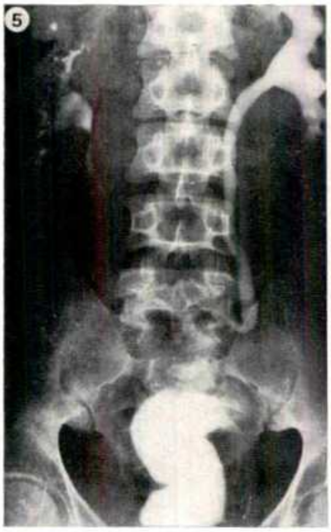

Fig. 5. I.V.P. A kink of the left ureter.

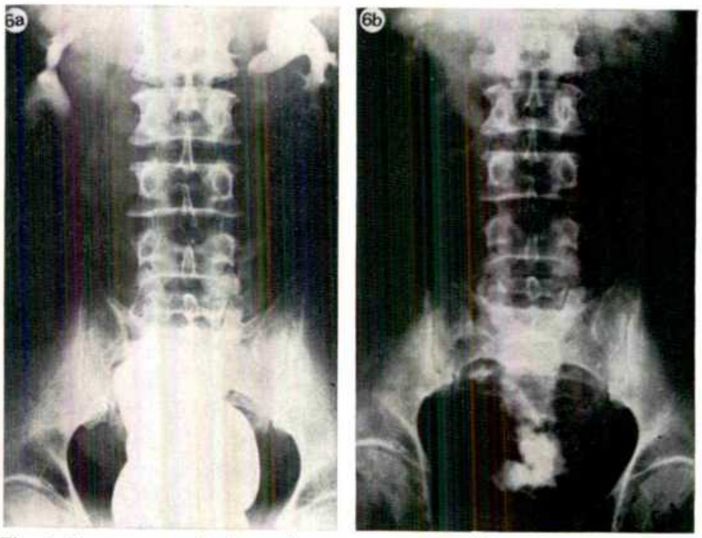

Fig. 6. Proctograms. **A**, Ascending proctography: bilateral procto-ureteral reflux. **B**, Post-micturition: almost complete evacuation.

Although the rectal bladder is a continent reservoir (Table IX) nocturnal leakage occurred in 40% of cases. Anal continence is dependent on an acquired capacity to suppress the natural urge to defaecate which requires normal neuromuscular control. The nature of the rectal contents is recognised by the somatic sensory apparatus in the anal canal (Duthie and Bennett, 1963). The internal anal sphincter is responsible for resting muscular control with the external sphincter acting only as an emergency reinforcement (Duthie, 1967). During sleep this emergency control is not working; small quantities of urine can pass, possibly being sensed as gas.

Table VII

Frequency of Micturition After Operation

	Day		Night	
Rate	No. of Patients	%	No. of Patients	%
Less than 2	11	18·3	25	41·6
2-3	31	51·6	18	30
4-5	10	16·6	12	20
6+	8	13·3	5	8·3

Table VIII

Capacity of Rectal Bladders (12 Cases)

	*St. DV.
Measured capacity	420 ± 80 ml
Voiding capacity	230 ± 50 ml

* St. DV. = Standard Deviation.

Social States of Patients with a Rectal Bladder

The patient with a terminal colostomy rapidly acquires the habit of regular evacuation once or twice a day, and management is simple. The use of a special collecting apparatus is unnecessary; a simple abdominal belt is all that is required. Table X shows the social state of 32 patients with a rectal bladder, 1 year after operation. It can be seen that 90% of patients surviving the operation are active and socially acceptable individuals.

Conclusions

We find the construction of a rectal bladder to be an excellent method of urinary diversion. Although it entails the formation of a colostomy, its management is easier than that of an ileal conduit and it does not require any special collecting apparatus.

Separation of faecal and urinary streams does of course reduce the hazards of urinary infection which are so common after simple uretero-colic anastomosis.

We prefer mucosa-to-mucosa anastomosis. The harmful effects of reflux are minimised by the low voiding pressure of the rectal bladder, and reflux itself is of course of less consequence as the faecal stream has been diverted. Stenosis is more likely to follow oblique implantation of the ureter and is more dangerous than reflux (Kuss *et al.*, 1970).

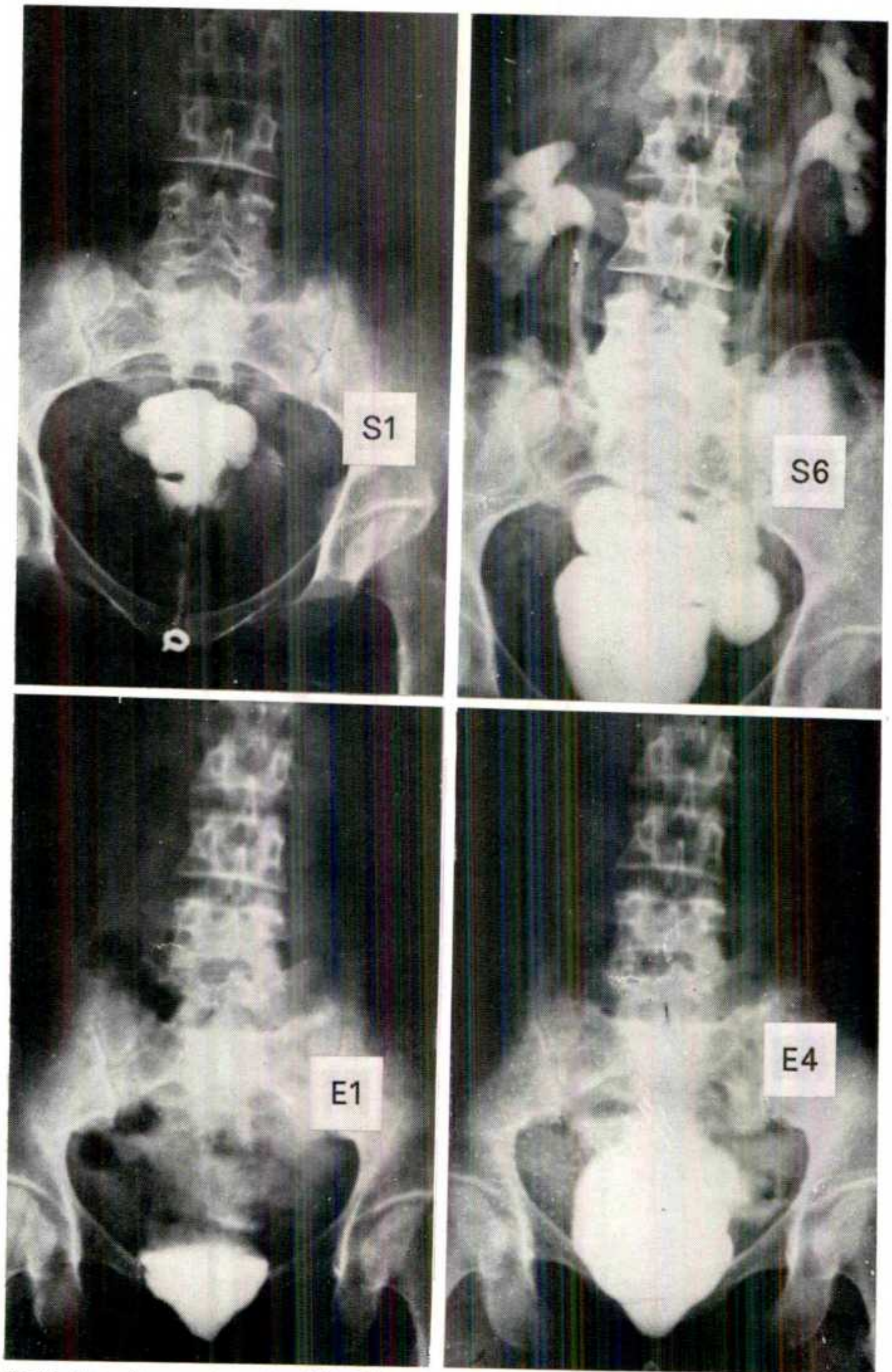

Fig. 7. Ascending proctography, "S": filling while patient was supine; "E": filling while patient was erect. *Note:* Earlier desire to void, and less functional capacity in the erect posture.

Nocturnal urinary leakage is fairly common but can be controlled to a large extent by fluid regulation. The capacity of the reservoir can be increased by dividing the bowel at least 7·5 cm above the rectosigmoid junction, thus decreasing postoperative frequency.

On balance, the procedure can be recommended as a standard method for many cases requiring urinary diversion.

Table IX

Continence

	Day		Night	
	Complete	Incomplete	Complete	Incomplete
No.	56	4	36	24
%	93·3	6·6	60	40

Table X

Social Status of 32 Patients
One Year after Surgery

	No.	%
Back to previous work	8	25
Back to lighter work	21	66
Invalid	3	9

Summary

89 patients suffering from carcinoma of the bladder treated by cystectomy and construction of a rectal bladder were reviewed.

The immediate postoperative mortality was 12·5%, most deaths being due to infection.

64 patients had been followed for 6 months to 3 years.

The 64 patients possessed a total of 115 kidneys, and there was radiological evidence of postoperative deterioration in 23 instances. Anastomotic stricture formation was the commonest complication.

Measurement of rectal bladder capacity showed the functional to be smaller than the anatomical. This was shown radiologically to be due to a change of posture; the capacity is greater when the patient is supine than when he is erect.

Nearly all patients were continent by day; leakage at night occurred in 40%

29 of 32 patients were at work 1 year after operation.

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The Use of Frusemide and Epsilon-Amino-Caproic-Acid in Transurethral Prostatectomy

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Epsilon-amino-caproic-acid (E.A.C.A.), a synthetic inhibitor of fibrinolytic activity, has been shown to be a safe and effective method of reducing blood loss following prostatectomy, McNichol *et al.* (1961), Anderson (1962), Vinnicombe and Shuttleworth (1966*a* and *b*), Kirkman (1967) and Gordon-Smith *et al.* (1972). The use of frusemide to promote a postoperative diuresis to prevent clot retention following prostatectomy has been claimed to have advantages over other forms of irrigation in terms of simplicity, safety and prophylaxis against renal failure, Jameson (1969), Essenhigh and Eustace (1969) and Williams (1972).

In this study the combined effect of E.A.C.A. and frusemide has been examined in a group of patients undergoing transurethral prostatectomy.

Methods

111 consecutive patients undergoing transurethral prostatectomy between September 1972 and March 1973 were studied, and all the patients were routinely given a postoperative frusemide diuresis. A pilot study was first performed with varying doses of frusemide and the electrolyte requirements were calculated by measuring the urinary losses over the first 24 hours postoperatively. The regimen shown in Table I was found to be the most satisfactory.

Table I

Frusemide	I.V. Fluid
40 mg I.V. at end of operation 20 mg I.M. after 2 hours and then 20 mg I.M./orally 4 hourly for 24 hours	Peroperative: 1 litre Hartman's solution + blood for losses > 500 ml Postoperative: N/S 500 ml alternating D/S 500 ml 4 hourly

(D/S = Dextrose Saline; N/S = Normal Saline)

Further blood transfusions or extra N/S were given if the clinical state indicated that this was necessary. The intravenous infusion was continued overnight until adequate oral intake was achieved.

E.A.C.A. was given to a randomised selection of patients, by double blind technique; the controls received matched N/S ampoules. 4 g of E.A.C.A. were infused during the operation and 1 g E.A.C.A. per hour (4 g/500 ml bottle) was given intravenously for the first 12 hours postoperatively, making a total of 16 g.

The transurethral prostatectomies were performed under general anaesthesia, supplemented by epidural anaesthesia in 2 cases. Resections were performed using the Storz 27·5 F resectoscope, irrigating with 1·5% glycine (Travenol). On completion of the prostatectomy a 22 F plastic Foley catheter was inserted into the bladder, the balloon inflated with 30 ml of sterile water and light traction applied to hold the balloon against the bladder neck. Continuous drainage into a plastic drainage bag with a non-return valve was instituted and the patient returned to the recovery ward, to remain there until satisfactory drainage was maintained, before returning to the main ward.

Blood loss was measured during the operation and during the first 24 hours postoperatively. A trial extraction of blood was first performed from both glycine and urine, and it was found that a 100% recovery could be attained. The intraoperative glycine washouts were collected, measured, thoroughly mixed, and an aliquot was removed for haemoglobin estimation. Similarly, the 24-hour urine collection was measured, mixed, and an aliquot removed for haemoglobin estimation. From the knowledge of these figures, and of the patient's haemoglobin, it was possible to calculate the blood loss.

Haemoglobin, urea and electrolytes measurements and mid-stream urine cultures were performed routinely, pre- and postoperatively on all patients. Careful observations were made for clinical evidence of cardiac failure or deep vein thrombosis. Difficulties in catheter management were recorded by the medical and nursing staff, noting whether the catheter needed aspirating, whether any washouts were required, when the catheter was removed, and whether re-catheterisation was necessary.

Results

The age, and mode of presentation of the patients were similar in both groups, as were the types of anaesthesia used. The weights of the resected prostate and the histology of the tissue removed were comparable. This is shown in Table II.

Table II

		E.A.C.A.	Control
Age		S.D. 68·9 ± 12·1 years	S.D. 66·0 ± 11·0 years
Presentation	Prostatism	35	36
	Acute retention	12	15
	Chronic retention	8	5
	Total	55	56
Anaesthetic	Spontaneous respiration	44	43
	Controlled ventilation	10	12
	Epidural anaesthesia	1	1
Weight		S.D. 18·2 ± 11 g	S.D. 17·6 ± 10·6 g
Histology	Benign hyperplasia	47	48
	Carcinoma	8	8

A reduction in blood loss of 57% over the first 24 hours postoperatively was noted in the group receiving E.A.C.A. This reduction is statistically significant at greater than 2 standard errors of difference. These losses are compared in Table III.

Table III

Blood Loss	E.A.C.A.	Control
Operative	S.D. 145·4 ± 136·2 ml	S.D. 115·9 ± 139·8 ml
Postoperative first 24 hours	S.D. 47·2 ± 47·5 ml	S.D. 109·4 ± 157·95 ml

The volume of irrigating fluid required was similar in each group, but the postoperative diuresis in the patients receiving E.A.C.A. was significantly less than the control group (>2 standard errors of difference). These volumes are shown in Table IV.

Table IV

	E.A.C.A.	Control
Volume of irrigating fluid	S.D. 11·4 ± 5·28 litres	S.D. 10·8 ± 6·0 litres
Diuresis first 24 hours	S.D. 3·870 ± 1·065 litres	S.D. 4·432 ± 1·129 litres

There were fewer problems with catheter management in the E.A.C.A. group. These are presented in Table V.

Table V

Catheter Management

	E.A.C.A.	Control
Washouts	7	10
Change of catheter	0	5
Return to theatre for evacuation of clot	0	1
Catheter removed	S.D. 2·09 ± 1·40 days	S.D. 2·26 ± 1·0 days

The postoperative infection rate was also lower in the E.A.C.A. group as shown in Table VI

Table VI

Infection

	E.A.C.A.	Control
Insufficient data	6 (11%)	7 (12%)
Infected preoperatively	10 (20%)	6 (12%)
Developed infection postoperatively	5 (13%)	8 (19%)

The duration of hospital stay was similar in both groups, 6·3 ± 3·2 days for E.A.C.A. group and 6·8 ± 3·3 days for control. There was no mortality or recorded thrombo-embolic episodes in either group within 3 months of the operation. Three patients given E.A.C.A. were re-admitted with secondary haemorrhage compared with 1 of the control patients.

Discussion

In this Unit approximately 250 transurethral prostatectomies are performed each year. The usual method of postoperative bladder drainage was a frusemide diuresis as outlined, and a 22 F plastic Foley catheter with light traction and continuous drainage. Whilst drainage in the main was satisfactory, it was noted that a significant number of patients required catheter attention; either aspiration of clot, washouts or even change of catheter. These problems usually arose in the first postoperative hour. A postoperative regimen has therefore been devised, adding E.A.C.A. to the frusemide diuresis in an attempt to minimise haemorrhage and catheter complications. This regimen has been compared with a control group receiving the frusemide diuresis alone. The combined effect of postoperative E.A.C.A. and frusemide has not previously been reported.

The peroperative blood losses recorded in this series correspond to those observed by other workers (Symes *et al.*, 1972) and were not influenced by E.A.C.A. However, the postoperative blood loss was significantly reduced in patients receiving E.A.C.A. as compared with those receiving a frusemide diuresis alone. As a result, less interference with the closed drainage system was required in the E.A.C.A. group compared with the control group. The control group, however, was still comparable with other series using continuous irrigation, continuous drainage and frusemide diuresis Symes *et al.* (1969), Essenhigh and Eustace (1969).

The greater the interference with a closed drainage system the higher the rate of infection. In this series the postoperative infection rate was lower in the group given E.A.C.A.—(13%) compared with controls (19%). The infection rates in both groups, however, were greater than have been reported elsewhere, Symes *et al.* (1972). This relatively high infection rate may have been due to the omission of chlorhexidine from the drainage system because of its interference with the estimation of blood loss.

One observation which requires further investigation is the significant reduction in diuresis in patients given E.A.C.A.

Summary

A randomised prospective clinical trial has been performed to assess the effectiveness of giving ε-amino-caproic-acid to patients routinely receiving a frusemide diuresis, following transurethral prostatectomy. A significant reduction in postoperative blood loss, and fewer problems related to catheter management and infection were noted in the group of patients receiving E.A.C.A.

We wish to thank Dr D. Pearce and Dr W. E. Waters for their help in devising the trial, Mr R. Rumble and Mr B. Howard for their technical assistance and the nursing staff of Southampton General Hospital for their co-operation.

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Prostatic Calculi as a Source of Recurrent Bacteriuria in the Male

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Minute calculi are frequently found in the prostate in men over 50 years of age (Joly, 1929; Riches and Muir, 1933); larger calculi are less common. In a study of 3,510 men of average age 56 years, Fox (1960) found an incidence of 13·8% of radio-opaque stones; of these 4% had associated urinary tract infection and 8·5% were stated to have prostatitis, though this was not defined. Renal calculi were noted to be present in 10·5% of men with prostatic stones. There have been few investigations into the relationship between prostatic calculi and recurrent urinary tract infection. It is possible that in these patients the stones act as a continuing source of bacteria in the same way as Nemoy and Stamey (1971) suggested in their study of renal stones. We report here 3 patients with relapsing bacteriuria in whom the infecting bacteria were grown from prostatic calculi.

Methods Used in Investigation of These Patients

Localisation of Infection by Ureteric Catheterisation

The method used is fully described by Eykyn *et al.* (1972) and is based on that described by Stamey, Govan and Palmer (1965).

Lower Tract Localisation

The method used is that described by Meares and Stamey (1968).

Serum Antibodies

The method used was the direct bacterial agglutination technique as described by Brumfitt and Percival (1964).

Culture of Prostatic Calculi and Prostatic Tissue

The calculi (or tissue) were shaken for about 1 minute in 8 successive 10 ml aliquots of nutrient broth. A standard loop (approximate volume of 0·006 ml) of the first broth washings and of the last broth washings was cultured on C.L.E.D. agar (Oxoid CM 301) and on blood agar incubated aerobically and anaerobically for 3 days. The object of the broth washings was to remove any contamination that might be present on the surface. The stone or tissue was then crushed in a sterile mortar using a few drops of nutrient broth, and a standard loopful of the crushings was cultured as above.

Results

The results for the various investigations performed on the 3 patients are shown in Tables I to III and Table IV shows the biochemical characteristics, antibiotic sensitivity patterns and serotypes of the organisms isolated.

Case Reports

Case 1. A 33-year-old man presented in August 1970 with a 3-month history of intermittent bilateral lumbar pain, day frequency, burning on micturition and night sweats.

Escherichia coli, sensitive to all antibiotics tested, was cultured from a mid-stream urine and excretion urography showed a cavity in the left kidney which communicated with the upper calyx, and atrophy of the upper pole. The right upper tract was normal. Numerous prostatic calculi were noted to be present (Fig. 1) and there was a small residual urine volume after micturition. No reflux was demonstrated on micturating cysto-urethrography. No acid fast bacilli were seen on smear or grown on culture from repeated early morning specimens of urine.

Localisation of infection by ureteric catheterisation showed bilateral renal infection (Table I) and an antibody titre of 1:1,280 to the infecting strain of *E. coli* was found in the patient's serum. He was treated with cephalexin for 2 weeks with symptomatic improvement, but over the next 2 years his urine was repeatedly infected with the same *E. coli* despite various courses of appropriate antimicrobial therapy. Two attempts were made to localise infection within his lower urinary tract (see Table II), but no proof of prostatic infection was obtained; on the first occasion only scanty urethral commensals were grown and on the second his urine was infected and a heavy growth of *E. coli* was obtained from all specimens. A further upper tract localisation in October 1972 was again suggestive of bilateral renal infection but the serum antibody titre could not be estimated because the *E. coli* persistently autoagglutinated. Endoscopy carried out in 1970 showed minor trabeculation of the bladder; 2 years later this had increased and definite bladder neck obstruction was present. A transurethral resection of prostate was performed on 16th October 1972, and most but not all of the prostatic calculi were removed. The crushed prostatic tissue was sterile on culture but the crushed stones yielded a heavy growth of the same *E. coli* as that repeatedly cultured from the urine. The patient was discharged with sterile urine on no antimicrobial therapy but urinary infection recurred within 1 month of surgery. Treatment with low dosage sulphamethizole (100 mg b.d.) was then started and his urine has remained sterile on this regimen for 9 months, his symptoms markedly improved, and when he was last seen he had no complaints.

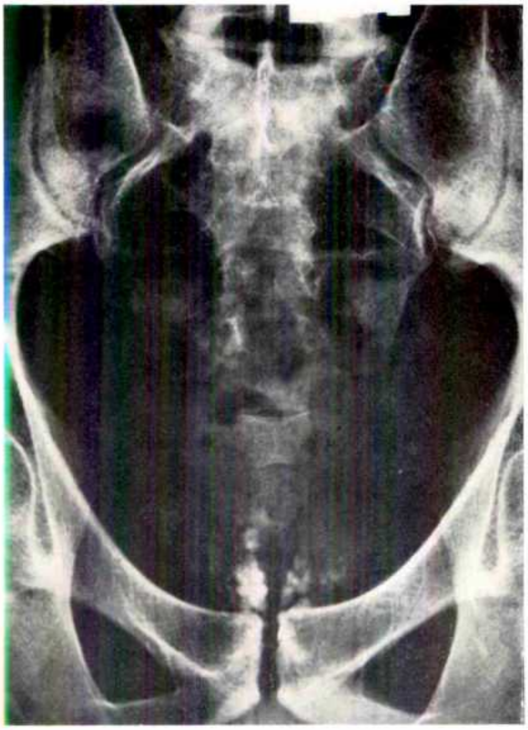

Fig. 1. Case 1.

Case 2. A 60-year-old man initially presented in 1968 with a 5-year history of left groin and testicular pain. He was found to have a small inguinal hernia which was repaired; at operation his testis was normal and a small epididymal cyst was aspirated. A routine urine culture before surgery yielded a heavy growth of *E. coli* (not serotyped) which was eradicated with ampicillin. He was seen at regular intervals over the next 3 years; within 1 month of operation his testicular pain had recurred and he also developed marked day frequency with some nocturia, perineal pain, low backache and dysuria. Prostatic tenderness was noted on several occasions. Urine cultures during this period showed recurrent infection with *E. coli*, usually with 2 fully sensitive strains. He received numerous courses of antimicrobial therapy. Mild bladder neck obstruction was found on endoscopy; excretion urography showed normal upper tracts but numerous prostatic calculi were noted and the radiographic appearance of these was similar to case 1 (see Fig. 1). A small residual volume of urine was present after micturition and no reflux was demonstrated on micturating cysto-urethrography. Lower tract localisation was attempted on 1 occasion only, but the patient's urine was heavily infected at the time (Table II). Upper tract localisation showed right renal infection with *E. coli* I and II (Table I) but no antibodies to these organisms were demonstrated in his serum. A transurethral resection of prostate and bladder neck was performed on 8th November 1971. The crushed prostatic calculi yielded a profuse growth of *E. coli* I and II and also a scanty growth of a further serotype *E. coli* III which was resistant to sulphonamide, ampicillin and cephaloridine, and which had never been cultured from his urine. The crushed prostatic tissue yielded only a scanty growth of all 3 strains (Table III). Despite surgery and continued treatment with cotrimoxazole, symptomatic bacteriuria recurred within 6 weeks; the patient also suffered persistent pain from epididymitis for which a left orchidectomy was performed in January 1972. He was re-admitted in December 1972 because of persistent dysuria, frequency, perineal pain and backache. A retropubic enucleation of the remaining prostatic adenoma was performed in January 1973; most of the remaining prostatic calculi were removed at this time and when crushed yielded a heavy growth of *E. coli* I. Only a scanty growth, also of this serotype, was obtained from the crushed prostatic tissue. Infection recurred within 1 month of surgery and although his urine can readily be

Table I

Upper Tract Localisations

			Bacterial Counts per ml Urine											
Case	Date	Organism	CSU	WB	RK1	RK2	RK3	RK4	RK5	LK1	LK2	LK3	LK4	LK5
1	21.9.70	*E. coli*	10^6	10^3	10^{4-5}	10^4	10^4	10^4	10^5	10^{4-5}	10^{4-5}	10^4	10^4	10^3
	9.10.72	*E. coli*	10^7	10^3	10^4	10^4	10^{4-5}	10^{4-5}	10^{4-5}	10^{2-3}	10^{2-3}	10^{2-3}	10^3	10^3
2	2.11.72	*E. coli* I and II	10^{4-5}	10^2	10^{2-3}	10^3	10^2	10^3	10^2	0	0	0	0	0

CSU = Cystoscopic specimens.
WB = Washed bladder.
RK = Right kidney, successive specimens 1-5.
LK = Left kidney, successive specimens 1-5.

Table II

Lower Tract Localisations

			Organisms per ml			
Case	Date	Organisms	VB1	VB2	EPS	VB3
1	28.1.72	Urethral flora	< 100	< 100	< 100	< 100
	13.10.72	*E. coli*	10^7	10^7	no specimen	10^7
2	27.10.71	*E. coli* I and II	10^7	10^7	no specimen	10^7

VB1-3 = Voided bladder specimens.
EPS = Expressed prostatic secretion.

rendered sterile and his symptoms controlled with cotrimoxazole, if this drug is discontinued the *E. coli* and the symptoms inevitably return.

Case 3. A 47-year-old man was first seen at St Thomas's Hospital in 1962 with a long-standing history of recurrent attacks of frequency and dysuria and a recent history of suprapubic and loin pain. At this time a mid-stream culture of his urine was reported to have grown *E. coli* (antibiotic sensitivity was not recorded) and an excretory urogram was normal. A minor anterior urethral stricture was found on instrumentation and this was dilated. The patient was not seen again until May 1972, when he was complaining of gross day frequency without nocturia, some hesitancy, slight dysuria and persistent loin and suprapubic pain. *E. coli* resistant to sulphonamide and ampicillin was grown from his urine. Excretion urography showed normal upper tracts and numerous prostatic calculi were present. There was a small residual urine volume after micturition. When admitted to hospital 1 month later his urine was sterile as a result of antimicrobial therapy and it was therefore not possible to undertake upper tract localisation.

Table III

Prostatic Calculi and Tissue

Case	Date	Urine from Endoscopy	Specimen	First Washing	Last Washing	Crush
1	16.10.72	No growth	Tissue	No growth	No growth	No growth
			Calculi	± *E. coli*	± *E. coli*	+ + + *E. coli*
2	6.11.71	No growth	Tissue	+ + *E. coli* I, II, III	+ *E. coli* I, II, III	+ *E. coli* I, II, III
			Calculi	± *E. coli* I, II, III	+ + *E. coli* I, II, III	+ + + *E. coli* I, II ± *E. coli* III
	4.1.73	No growth	Tissue	± *E. coli* I, II	No growth	± *E. coli* I, II
			Calculi	+ *E. coli* I, II	No growth	+ + + *E. coli* I, II
3	30.10.72	No growth	Tissue	No growth	No growth	No growth
			Calculi	± *E. coli*	No growth	+ *E. coli*

± Few colonies; + scanty growth; + + moderate growth; + + + heavy growth.

Table IV

Case	Organism	Biochemical Characteristics	Antibiotic Sensitivity	Serotype
1	*E. coli*	*ONPG negative	Fully sensitive	0 rough H1
2	*E. coli* I	ONPG negative (large mucoid colony)	Fully sensitive	04 K12 H-
	E. coli II	ONPG late positive (smaller flat colony)	Fully sensitive	0 unidentifiable with 149 antisera
	E. coli III	ONPG positive	Resistant to ampicillin and cephaloridine	06 K2ac H3
3	*E. coli*	ONPG positive	Resistant to ampicillin and sulphonamide	083 K? H31

* ONPG O-nitrophenyl-β-D-galactopyranoside test to detect potential lactose fermenters.

Lower tract localisation was not attempted either. In October 1972, endoscopy showed trabeculation of the bladder with marked bladder neck obstruction but no urethral stricture was present. A transurethral resection of prostate and bladder neck was carried out. The same serotype of *E. coli* as had been previously isolated from the urine, was grown from the crushed prostatic calculi, although the crushed prostatic tissue was sterile (Table III). Following surgery, infection recurred within 1 month, and was controlled only by continuous therapy with cotrimoxazole but the patient continues to complain of frequency and difficulty related to the development of a bulbar stricture.

Discussion

There seems little doubt that the prostatic calculi harboured the strains of *E. coli* responsible for the recurrent urinary tract infections in these 3 patients. It is interesting that, whereas the crushed calculi yielded large numbers of organisms on culture, only small numbers were grown from the culture of the crushed prostatic tissue. This would seem to suggest that it was the calculi rather than the prostatic tissue itself which was the main source of the infecting organism. However, at the time of surgery all 3 patients were either currently receiving an antibiotic or had very recently been treated with one and it is possible that this could perhaps have influenced the results of culture of the prostatic tissue.

Meares and Stamey (1968) consider that chronic bacterial prostatitis characterised by the presence of small numbers of bacteria in the prostatic secretion is an important cause of recurrent urinary tract infection in the male. The patients we have described had the symptoms of "clinical" chronic prostatitis and all had symptomatic recurrent bacteriuria but we failed to recover the organisms responsible for the repeated episodes of urinary infection from the prostatic secretion in the 2 patients in whom this was attempted. In 2 of the 3 patients the prostatic tissue obtained at operation was sterile. Nemoy and Stamey (1971) have shown that when renal stones are associated with infection, the infecting bacteria reside within the stones and are therefore protected from the action of antimicrobial agents. Our findings would suggest that this may also apply to prostatic calculi.

Meares and Stamey (1968) suggest that prostatic infection may be a cause of renal infection and stones and describe a patient in whom this was thought to have occurred. In cases 1 and 2 renal infection was demonstrated; in case 1 both kidneys were infected on upper tract localisation and the urogram was abnormal on the left, and in case 2 the right kidney was shown to be infected though the urogram was normal. It could be argued that infection within the kidney was the original source of relapsing bacteriuria which then became lodged in the prostatic stones, but it is unusual in patients with chronic infection with proven renal involvement for the urogram to be normal as in case 2.

Although prostatic calculi are common, they are usually entirely asymptomatic. We have cultured crushed prostatic calculi from 8 patients who did not have a history of recurrent urinary tract infection; no organisms were grown in 6 and *Staphylococcus albus* in 2. Although very small numbers are involved here it seems unlikely that *E. coli* commonly resides in prostatic stones in the absence of recurrent urinary tract infection. It is suggested that once bacteria become established within prostatic stones, the stones act as a persistent nucleus of infection and are protected from the action of antimicrobial agents. Antibiotic treatment in these patients can at best only be suppressive, relapses occurring whenever drugs are discontinued and sometimes despite drugs.

Summary

Three patients with recurrent symptomatic bacteriuria are presented, in each of whom radio-opaque prostatic calculi were present and were shown to harbour the infecting organism.

We thank Dr B. Rowe for kindly typing the *E. coli* strains and Miss C. Jenkins for careful technical assistance.

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The Crystalline Composition of Prostatic Calculi

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Very few prostatic calculi have been analysed by the X-ray powder method, a technique which gives the exact nature of the crystalline material present and not, as in chemical analysis, a jumble of ions which are often impossible or difficult to relate. Huggins and Bear (1944) studied 2 true prostatic stones using this method, found the chief constituent was the same as that of bone, but wrongly reported it as being tricalcium phosphate instead of apatite probably because of the confusion existing then over the composition of the different calcium phosphates. No other crystalline material was found. Over the last 7 years, we have received 28 prostatic calculi for analysis by X-ray diffraction. The results are summarised here since they show the presence of a calcium phosphate not previously reported in prostatic calculi as well as providing the first comprehensive X-ray analysis of this type of stone.

Material and Method

The stones ranged in weight from 0·004 to 22·5 g and came from patients whose ages ranged from 30 to 92 years. They were analysed using the techniques described in an earlier paper (Lonsdale, Sutor and Wooley, 1968).

Results

The crystalline compounds identified in the stones are carbonate-apatite, hydroxyapatite, whitlockite (β-$Ca_3(PO_4)_2$), calcium oxalate monohydrate and dihydrate, anhydrous uric acid, uric acid dihydrate, struvite ($MgNH_4PO_4.6H_2O$), cystine and ammonium acid urate. The composition of each stone is given in the Table. 14 calculi consist of one or more of the 3 calcium phosphates (carbonate-apatite, hydroxyapatite and whitlockite). There are 6 stones composed of calcium oxalate+calcium phosphate, 3 of uric acid+calcium oxalate, 2 of calcium oxalate, 2 associated with infection by urea-splitting organisms in that they contain carbonate-apatite+struvite, and one of cystine.

Discussion

Endogenous prostatic calculi are found in the substance of the prostate and form from the prostatic fluid while the exogenous ones are in the urethra or some existing pocket in the prostate and are derived primarily from urine. Information as to type was provided in the case of only 3 of the stones analysed here and these were of the endogenous variety consisting of apatite+whitlockite. However, most of the endogenous prostatic calculi in this collection can be differentiated by their composition. Inspection of tables giving the composition of prostatic fluid (Sunderman and Boerner, 1949) suggests that of all the constituents only apatite and whitlockite can form in this secretion. Furthermore, a comparison of the frequency of occurrence of the different composition types with those in collections of adult lower urinary tract stones (Sutor, Wooley and

Illingworth, 1974*a* and *b*) shows that in the latter group, whitlockite is a rare constituent and only a small proportion of stones consists entirely of apatite while in the prostatic calculi whitlockite is a major constituent and pure apatite stones are extremely common. Endogenous prostatic calculi are therefore composed of apatite or apatite + whitlockite like stones from salivary glands (Jensen and Danø, 1952). These compounds are also important constituents of dental calculi (Jensen and Rowles, 1957) but rarely occur in gallstones (Sutor and Wooley, 1971). Whitlockite had not been previously reported as occurring in prostatic calculi. Its identification has now established the similarity in composition between salivary and prostatic stones and suggests apatite and whitlockite are likely to be the representative constituents of glandular calculi.

Table

Composition of the Prostatic Calculi

Constituents Present	No. of Stones	Constituents Present	No. of Stones
F1 + F4	5	C1	1
F1	4	C1 + C2	1
F2	2		
F1 + F2	2	D	1
F2 + F4	1		
		A1 + C1	1
C1 + F1 + F2	2	A1 + C1 + C2	1
C1 + F2	1	A1 + A2 + C1 + C2	1
C2 + F1	1		
C1 + C2 + F2	1	C1 + F1 + F2 + G2	1
C1 + C2 + F1 + F2	1		
		B + F1 + G2	1

Key:
A1 = anhydrous uric acid, A2 = uric acid dihydrate,
B = ammonium acid urate, C1 = calcium oxalate monohydrate,
C2 = calcium oxalate dihydrate, D = cystine,
F1 = carbonate-apatite, F2 = hydroxyapatite,
F4 = whitlockite, G2 = struvite.

Summary

The composition of 28 prostatic calculi has been determined by X-ray diffraction. 14 stones consisted entirely of 1 or more of the following calcium phosphates—carbonate-apatite, hydroxyapatite and whitlockite. Most of these are likely to be true or endogenous prostatic calculi formed from the prostatic fluid. The other 14 stones contained compounds which can precipitate from urine but are unlikely to precipitate from the prostatic secretion. These are the exogenous type forming at least in part from urine. Whitlockite which was found to be a major constituent of the true stones has been identified in them for the first time. Its discovery shows that salivary and prostatic calculi are similar in composition in that they consist of apatite or apatite + whitlockite.

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·The Response of Prostatic Fluid pH in Inflammation

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Winningham, Nemoy and Stamey (1968) were the first to draw attention to the significance of the pH environment of the prostatic acini and ducts in respect of their penetration by drugs and in particular by antibiotics. Using the dog as an experimental model they found that the prostatic epithelium appeared to act as a barrier to the passage of antibiotics and antibacterial agents from the plasma to the prostatic fluid. Subsequent work (Stamey, Meares and Winningham, 1970), again carried out on the dog, showed that the basic macrolides, erythromycin and oleandomycin, not only penetrated into the prostatic fluid but were concentrated within it to several times the simultaneous plasma level. This phenomenon was accounted for by the principles governing the passage of drugs across biological membranes with particular reference to the role of non-ionic diffusion of weak acids and bases between membranes with different hydrogen ion concentrations since almost all antimicrobial drugs are either one or the other.

The pH of the fluid in the prostatic acini and ducts has been found both in the experimental animal and in the normal human to vary between 6·2 and 6·5. This compares with a plasma pH of 7·4. The presence of a pH gradient of considerable magnitude across prostatic epithelium introduces the phenomenon of ion trapping which, according to Stamey *et al.* (1970), is one of the factors involved in the concentration of the basic macrolides in prostatic fluid. The principles of this phenomenon are summarised in Figure 1. A basic antibiotic with high pKa is unionised in the tissue fluid with its pH of 7·4 and the cell membrane of the prostatic epithelium is therefore relatively permeable to its molecules; having passed into normal prostatic fluid with its pH of 6·5 this antibiotic becomes ionised and in the ionised state finds the cell membrane of the prostatic epithelium relatively impermeable to its passage back into the tissue fluid. The molecules are therefore "trapped". If the prostatic fluid had a pH equivalent to that of the tissue fluid a similar basic antibiotic would remain unionised within the prostatic acini and ducts and therefore in a state which would allow its diffusion back into the tissue fluid. Concentration of the antibiotic would therefore be unlikely to take place.

From the findings of Stamey *et al.* (1970), and assuming a pH in the prostatic fluid of 6·6, it appeared that the ideal antimicrobial drug for the treatment of prostatitis was a lipid soluble base with a pKa of 8·6 or greater and a maximum biological action at a pH of 6·6.

Reeves and Ghilchik (1970), using dogs prepared by a technique similar to that suggested by Dunn and Stamey (1967), assayed the penetration of the prostatic fluid by the drug trimethoprim. Using a derivation of the Henderson-Hasselbach equation (Jacobs, 1940) the predicted ratio of trimethoprim concentration in prostatic fluid and plasma was 3·3 : 1, assuming pH values of 6·6 and 7·4 respectively; in the assays carried out on dogs the ratio of drug concentrations was found to approximate the theoretical values. Further studies on the secretion of antibiotics into the prostatic fluid of the dog have been carried out by Reeves *et al.* (1973), in which it was found that 7-chlorolincomycin was concentrated within the prostatic fluid and that lincomycin and chloramphenicol achieved a concentration equal to that of the serum.

It is significant that in all of these experiments the canine model was used and furthermore the prostate gland was not inflamed. The assumption has been made that similar circumstances apply in the human whose gland is the seat of inflammation.

This paper draws attention to pH changes in human prostatic fluid in the presence of signs of inflammation and discusses briefly the implication of this.

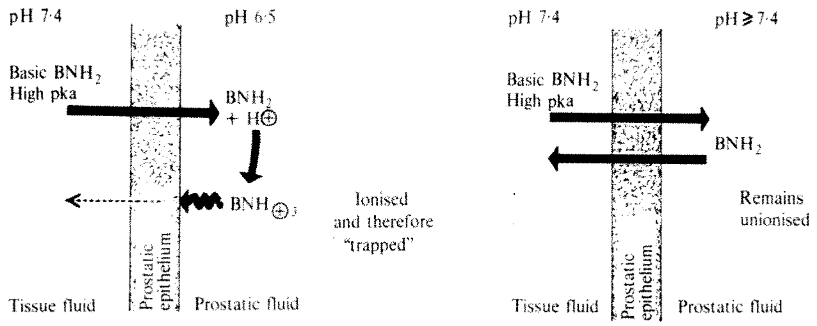

Fig. 1. Penetration of a basic antibiotic into the prostatic fluid at pH 6·5 and, on the right, at a pH of 7·4 or greater. In the latter instance, although the antibiotic may penetrate, it will not be concentrated within the fluid.

Materials and Methods

Expressed prostatic secretion (EPS) was obtained by a standard method after initial (VB1) and mid-stream (VB2) urine specimens at routine examination on a series of patients. Some of these had no demonstrable prostatic disease allowing an assumption of normal EPS. Others had prostatitis of varying acuteness, this diagnosis being made in the presence of a symptomatology of urinary frequency, dysuria, perineal and groin pain and with the finding on direct microscopy of the EPS of more than 10 leucocytes per high power field (HPF) throughout a specimen (Blacklock, 1970). Quantitative bacteriology was done on all of these specimens, the results showing the variation commonly found in this condition (Table).

Initially the pH was estimated using Camlab Duotest pH papers (Camlab Ltd, Cambridge) in the range pH 5·0 to pH 8·0; the results could be obtained to within 0·3 of a pH unit. It is well known that complex biological solutions may produce errors in pH measurements using such techniques. These values were therefore checked using a Radiometer pH Microelectrode (Radiometer E5021, V. A. Howe, London). The microelectrode required only 0·2 ml of fluid and the pH of the samples was measured at a constant temperature of 37°C.

The 2 techniques of measuring the pH were compared and a correlation co-efficient of 0·97 was obtained, allowing the assumption that the Duotest pH paper was a reliable method for further estimations of the pH of EPS. A larger series of samples was investigated using this method since it was both simple and rapid. The EPS was tested immediately after production and without delay to minimise the possibility of pH being influenced by cooling.

Results

EPS containing fewer than 10 leucocytes per HPF was found to have a pH varying between 6·1 and 7·7 (mean, 6·6). There was therefore similarity in these specimens with normal canine prostatic fluid. (Fig. 2) In the series of fluids showing more than 10 leucocytes per HPF, there was a variable increase in pH. In general, the greater the number of leucocytes, the higher the pH and in the presence of a pronounced leucocyte response pH was as high as 8 (mean, 7·7) (Fig. 2 and Table).

With the inaccuracies inherent in leucocyte counting in specimens of EPS including the possibility that expression of the acinar and duct content may be incomplete and the sample not therefore representative, there is no validity in equating the number of leucocytes present with a specific pH change. It is nevertheless apparent (Table) that leucocyte responses in excess of 20 per HPF were accompanied by pH changes to 7·4 or greater. In the more acute cases, (Cases 2, 3, 4, 6, 9, 10 and 12, Table) there was the confirmation of bacterial prostatitis in the cultures of the EPS or in cultures of both the EPS and the urine specimens. In the less acute cases, (Table, Cases 1, 5, 8 and 11) bacteria were either present in small numbers or absent. The raised pH of the EPS appeared to be independent of whether bacteria were present or not. In Case 7

Table

			Expressed prostatic secretion (EPS)			Urine Bacteria per ml	
Case	Symptoms	Date	Leucocytes per 1/6 field	Bacteria per ml	pH	VB1	VB2
1	+	April '73	20-30	0	8	0	0
	±	June '73	15-20	S. Albus 2,000	7·4	0	0
	−	July '73	< 10	0	7	0	0
2	+ +	—	> 100	E. Coli 100,000	8	E. Coli 100,000	E. Coli 50,000
3	+(E)	Oct '72	15	S. Pyog. 100,000	7·4	0	0
	+	Nov '72	30	0	7·4	0	0
	±	Dec '72	10	E. Coli 100,000	7·1	0	0
	−	Jan '73	< 10	0	7	0	0
4	+(E)	June '72	50	Ps. pyocyan. 100,000	7·7	0	0
	±	July '72	< 5	0	6·5	0	0
5	+	June '73	> 30	0	8	0	0
	−	Aug '73	15	S. Albus 4,000	6·8	0	0
6	+(E)	May '72	> 50	E. Coli 100,000	7·7	E. Coli 50,000	E. Coli 5,000
	−	July '72	< 2	0	6·5	0	0
7	+	Aug '72	< 5	E. Coli 100,000	6·5	0	0
	−	Sept '72	0	0	6·5	0	0
8	+	June '72	50	0	7·8	S. pyog. 50,000	S. pyog. 2,000
	−	Aug '72	10	0	6·5	0	0
9	+	Nov '71	> 50	E. Coli 100,000	8	E. Coli 100,000	E. Coli 50,000
	±	Dec '71	< 2	E. Coli 10,000	6·5	0	0
	−	Oct '72	< 10	0	7·1	0	0
10	+ +	Mar '73	> 100	0	8	E. Coli 20,000	E. Coli 2,000
	±	Mar '73	< 10	0	7·7	0	0
	−	June '73	10	0	6·8	0	0
	−	Aug '73	< 2	0	6·5	0	0
11	±	Jan '73	> 30	0	7·4	0	0
	±	Jan '73	15	0	7·1	0	0
	±	Feb '73	5	0	6·8	0	0
	−	June '73	0	0	6·2	0	0
12	+ +	April '73	50	E. Coli 100,000	7·4	E. Coli 100,000	E. Coli 100,000
	±	May '73	20	0	7·4	—	—
	−	June '73	< 2	S. Albus 11,000	6·5	0	0
	−	Aug '73	< 2	0	6·5	0	0

(Table) a culture of 100,000 *E. coli* in the EPS co-existed with a pH of 6·5; in this case, the leucocyte count was less than 5 per HPF. In summary, there was no obvious correlation between the quantitative bacteriology of the EPS and its pH, but there appeared to be a direct relationship between the intensity of the cellular inflammatory response and a rise in pH.

This pH change appears therefore to be an accompaniment of the inflammatory response of the prostatic acini and ducts, and therefore of "prostatitis", whether this be bacterial or not. A possible alkalinising effect in these circumstances of "contamination" of the EPS by fluid from the ejaculatory ducts or seminal vesicles was felt to have been excluded by the absence of sperms from all of these specimens.

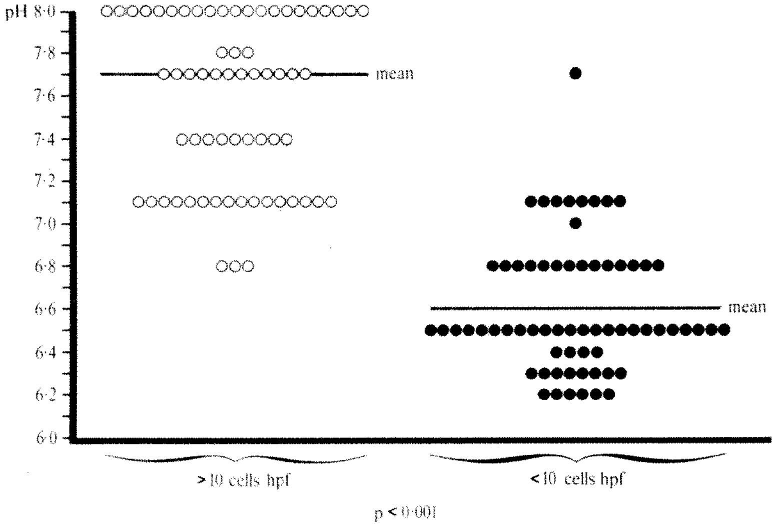

Fig. 2. Prostatic fluid pH response in inflammation.

During the course of resolution from inflammation, the pH was found to return slowly to the normal level. In this respect, since the pH tended to subside more slowly than the cellular inflammatory response, it was possible to have a prostatic fluid in which there were few pus cells present but in whom the pH had not yet returned to normal although it was less than the pH during the acute phase. This latter phenomenon was useful in the clinical assessment of patients who had received antibacterial therapy for a time before reaching hospital and in whom the leucocyte response of the EPS had been modified; in these, the pH generally remained higher than the normal mean value of 6·6 (Table, Cases 1, 3, 9 and 10).

Ludvik (1964) observed a similar change in the pH of EPS in his investigation of cases of chronic prostatitis.

Discussion

These findings show that in inflammation, whether this is of bacterial origin or not, the pH milieu conferred on the prostatic acini and ducts by the prostatic fluid is approximately the same as, or higher than, that of plasma and tissue fluid. The pH gradient between the tissue fluid and prostatic acini will therefore be minimal or non-existent and may even be reversed in those cases in whom the pH is 8.

Since this phenomenon has been shown to be an accompaniment of an inflammatory reaction within the EPS it could be applied as the basis of a simple colorimetric diagnostic test for "prostatitis". It has, however, much greater significance in the consideration of antibiotic concentration in the gland acini and ducts in the light of the work previously done in this respect (Winningham *et al.*, 1968; Stamey *et al.*, 1970; Reeves and Ghilchik, 1970).

The assumptions regarding concentration of antibiotics in the acini and ducts of the prostate which have been made on the basis of the pH of the prostatic fluid from experiments on the normal dog prostate (Winningham *et al.*, 1968; Stamey *et al.*, 1970; Reeves and Ghilchik, 1970) are therefore not valid when the prostate is in a state of inflammation. In these circumstances the ion-trapping phenomenon will not be a feature and the prostatic fluid concentration of drugs such as trimethoprim will theoretically be less than the concentrations found during the dog experiments (Fig. 1). The theoretical extent of this can be seen from the graph in Figure 3 (Reeves *et al.*, 1973). From this it is apparent that whilst achieving a concentration 4 times

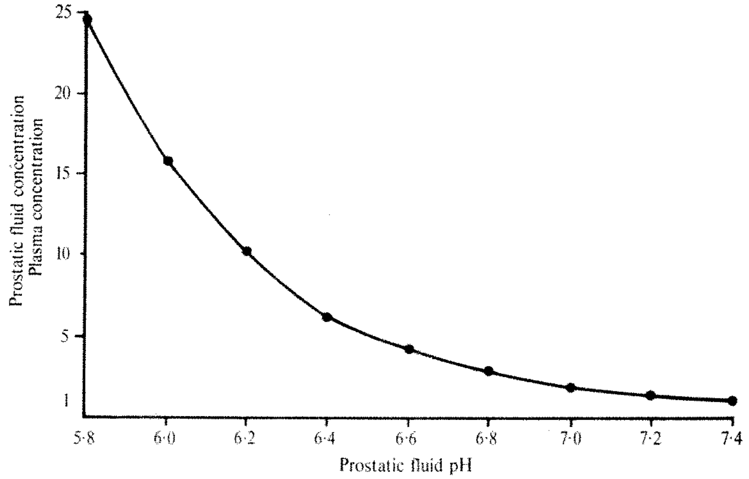

Fig. 3. Graph showing the theoretical changes in the prostatic fluid concentration: plasma concentration ratio (R) with changes in prostatic fluid pH for a basic antibacterial drug assuming a pKa of 7·6.
Values for R were determined from the formula

$$R = \frac{1 + 10^{pKa - pH\ (\text{Prostatic fluid})}}{1 + 10^{pKa - pH\ (\text{Plasma})}};$$

(Reeves, *et al.*, 1973).

that of plasma in the prostatic fluid at a pH of 6·6, an antibiotic will be present in a concentration little more than that of the serum when the prostatic fluid pH is 7·4. A preliminary series of specimens of human prostatic fluid have been assayed (Reeves, 1974) and these confirm that trimethoprim concentration in the prostatic fluid has been less than that found in the canine experiment. Nielsen and Hansen (1972) have also carried out assay of trimethoprim in human prostatic fluid and in prostatic tissue. They found that the concentration of the prostatic fluid was higher than in the plasma in 3 of 4 cases but the difference was not as great as that found in the dog experiment. The prostatic fluid specimens were obtained from glands which do not appear then to have been the seat of inflammation.

The pH of the prostatic fluid is not only significant to the antibiotic concentration in the acini and ducts of the prostate but is also important for its influence on the biological activity of the antibiotic; slight variation in pH may considerably alter this (Reeves *et al.*, 1973).

Since this paper devotes itself to noting pH changes in human prostatic fluid in states of inflammation, discussion has been confined to a consideration of the possible behaviour of antibiotics in these particular circumstances. It is not the purpose here to broaden the discussion to include the additional factors of the lipid solubility and protein binding of antibiotics which are so important in antibiotic diffusion. From the findings, however, it is clear that further assay work is required using human prostatic fluid from cases of prostatitis to establish the penetration and concentration of various antibiotics within the prostatic acini and ducts. Furthermore, consideration has also to be given to the influence of the pH on the biological activity of the antibiotic once present within the prostatic fluid. At this stage it seems likely that effective therapy of prostatitis will require a combination of antibiotics selected for their ability to penetrate the prostatic fluid in effective concentration and with a maximum biological activity between pH 7 and 8.

Summary

Expressed prostatic secretion (EPS) was obtained both from the uninflamed human prostate and from cases of acute and subacute prostatitis in the course of routine clinical examination.

In addition to microscopy and bacteriological examination, the pH of this fluid was tested using both Camlab Duotest pH papers (Camlab Ltd, Cambridge) and a Radiometer pH Microelectrode.

Specimens of EPS from the normal gland were found to have a mean pH of 6·6 and were therefore similar in this respect to normal canine prostatic fluid. In a series of specimens from cases of prostatitis, there was a variable increase in pH, the mean being 7·7.

The implications of this finding are briefly discussed in relationship to the concentration of antibacterial agents within the prostatic acini and ducts and their biological activity.

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Technetium-99M Polyphosphate Bone Scanning in Carcinoma of the Prostate

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With the introduction of ^{99m}Tc-technetium stannous polyphosphate (^{99m}Tc-P.P.) (Subramanian and McAfee, 1971) bone scanning has received considerable impetus. Previous reports have detailed the clinical use of bone scanning in metastatic carcinoma of the prostate using variously ^{85}Sr, ^{87m}Sr and ^{18}F (Charles and Sklaroff, 1964; Morgan and Mills, 1968; Williams, Blahd and Wetterau, 1968 ; Legge *et al.*, 1970 ; Roy *et al.*, 1971; and Robinson and Constable, 1973).

This investigation was designed to define the value of ^{99m}Tc-P.P. in patients with newly diagnosed carcinoma of the prostate. The advantages of ^{99m}Tc-P.P. relate to its ready availability, the simplicity of its preparation from generator produced ^{99m}Tc-pertechnetate, and, as relatively large doses may be safely administered, the high yield of information density in the resulting scan.

Patients and Methods

100 unselected and previously untreated consecutive patients referred to the Dr W. W. Cross Cancer Institute with biopsy proven carcinoma of the prostate were examined by radiographic skeletal survey and bone scan. Serum acid phosphatase estimations were made (Babson and Phillips, 1966).

Bone scans were obtained with an Ohio Nuclear 12·5 cm dual probe rectilinear scanner operated in minification mode and supplementary gamma camera scintiphotographs obtained where necessary with a Nuclear Chicago Pho Gamma III or H.P. scintillation camera. Bone scans were usually obtained within 1 month of the initial diagnosis of carcinoma of prostate and in 71% of patients were obtained within 2 weeks or less of histological diagnosis. The dose of ^{99m}Tc-P.P. (New England Nuclear) varied between 12 and 14 mCi which has been calculated to result in a radiation dose to the skeleton of approximately 0·45 rads (Subramanian *et al.*, 1972). Scans were obtained 4 hours after intravenous injection of the tracer.

The 100 patients investigated represent 82% of all patients in Northern Alberta diagnosed as having prostatic carcinoma during the period of study from 15th August 1972 to 22nd June 1973. The mean age of the patients was 69·7 years, with a range of from 50 to 90 years.

Skeletal radiographs, which included the skull, axial skeleton, pelvis and any scan positive sites, were interpreted independently and then reinterpreted in the light of bone scan findings.

Results

18 patients had evidence of bony metastases detected on the initial reading of the radiographs. This figure increased to 22 when the radiographs were again interpreted in the light of abnormal scan findings (Table I). This difference is significant ($p < 0{\cdot}01$). 2 of the additional 4 patients were previously considered to have equivocal radiographs.

However, a total of 34 patients had abnormal bone scans. This further difference is very significant ($p < 0{\cdot}001$).

Table I

Carcinoma of the prostate at time of initial diagnosis

	Bone Metastases	
100 Patients	Positive	Equivocal
Skeletal X-rays: first reading	18	6
Skeletal X-rays: read in conjunction with bone scan	22	0
^{99m}Tc-P.P. bone scan	34	3

Bone scans prove to supplement radiography in 3 important ways:

(*a*) by representing a relatively easy "search-and-find" task they draw attention to radiographic lesions otherwise overlooked in the more complex "search-and-find" task represented by a conventional radiographic skeletal survey.

(*b*) by detecting lesions in areas which are relatively blind to radiography, for example at the cervico-dorsal junction.

(*c*) by detecting lesions not detectable by conventional radiography.

In this series it has not been considered justifiable to resort to bone biopsy at the sites of positive scan findings. These patients are being followed. To date, of the 12 patients with positive bone scans and negative radiographs, 7 had developed radiographic evidence of metastatic disease to bone at precisely those sites anticipated by the initial bone scan (Fig. 1). Of the remaining 5 patients 3 had elevated serum acid phosphatase concentrations at least suggesting the presence of disseminated disease.

In 1 patient reported as scan positive, the bone scan abnormality of increased uptake adjacent to a sacro-iliac joint was overlooked initially. It was noted retrospectively when a subsequent scan was clearly positive at this site at which time the radiograph was positive. Otherwise there were no false negative scans *vis-à-vis* the radiographic findings.

The 3 equivocal scans were considered as thus because the only abnormality was a single area of increased uptake of the tracer of questionably abnormal extent. Follow up has not suggested that these were positive findings, and in 1 of the patients a repeat scan was considered to be normal.

Of the 6 patients with equivocal radiographs 2 were considered positive in the light of scan findings, and 4 negative. Follow up confirms this analysis.

The importance of radiological correlation with sites of abnormal uptake of the tracer must be emphasised. In 6 patients an abnormal scan was found, upon appropriate correlation, to be accounted for by Paget's disease of bone, apophyseal osteoarthrosis or osteoarthrosis of the hip. In reporting the results such scans are described as negative in the absence of other abnormal findings.

^{99m}Tc-P.P. is in part excreted in the urine, and, despite the tomographic effect of rectilinear scanning with a focused collimator, the full bladder still present after voiding in some patients with prostatic carcinoma afforded some difficulty. This difficulty was overcome by the use of the flexibility inherent in the gamma camera in providing oblique and lateral views of the bony pelvis. Severe obstructive uropathy involving the upper collecting systems was recognised, by virtue of the urinary excretion of the tracer, in 3 patients but was no surprise to the physician concerned.

The acid phosphatase concentrations in the patients studied are tabulated (Table II). There is

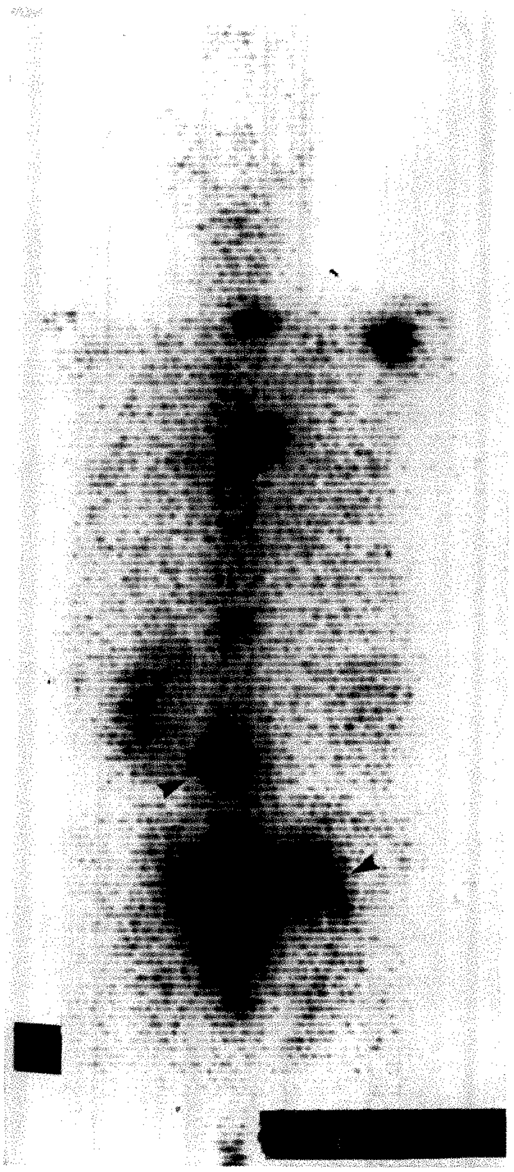

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Fig. 1. Part of a posterior probe bone scan in a patient with newly diagnosed carcinoma of prostate demonstrating focal sites of abnormal uptake of tracer. Note concentration of the radiotracer in the kidney, particularly the right.

a positive correlation (($\chi^2 = 54$, df = 3) between metastatic disease to bone and the serum acid phosphatase concentration (Table II).

The distribution of metastases determined from the bone scan findings (Fig. 3) indicates that, as might be expected, there is a preponderance of involvement of the pelvis. The cumulative incidence is intended to show that, while more distant metastases are observed, their detection outside of the pelvis, axial skeleton and ribs did not provide additional information in deciding the management of the patients in this series.

Table II

Serum acid phosphatase concentrations in international units. Laboratory normal limits 0 to 2

	X-ray positive	X-ray retrospectively positive	X-ray equivocal	X-ray negative
Scan positive	Number **18** limits 2·1-297	**4** 1·5-46·2	**2** 2-2	**10** 1·6-19·8
Scan equivocal or negative			**3** 1·2-2·2	**63** 1·2-5·3

Discussion

In selecting patients for radical treatment of carcinoma of prostate it is necessary to define if metastatic disease is present as accurately as possible. In the Dr W. W. Cross Cancer Institute the treatment of choice is radical radiotherapy in those patients aged 75 or less and having no evidence of disseminated disease (Roy, Cassady and Bagshaw, 1973). Radical radiotherapy was carried out in 31 of the patients included in this series, that is 67% of those without evidence of metastatic disease on the bone scan.

The evidence presented here suggests that bone scanning is of considerable importance in selecting patients for radical treatment.

While the acid phosphatase concentrations tend to correlate with the bone scan findings (Table II) it will be clear that the acid phosphatase would not of itself be an adequate index of metastatic disease. Of the 22 patients with scan and radiographic evidence of metastatic disease at diagnosis 6 had serum acid phosphatase concentrations of less than 3 international units.

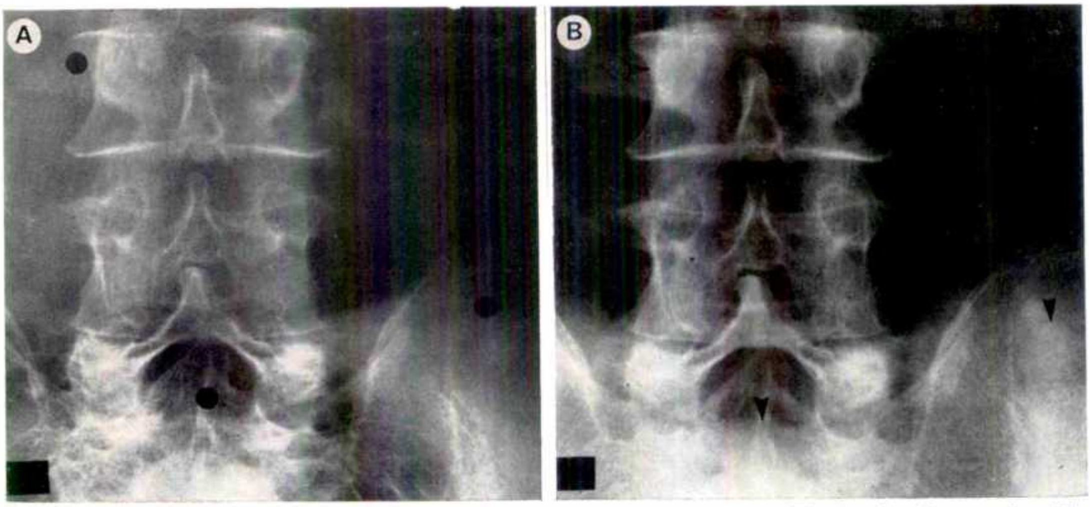

Fig. 2 A. An AP radiograph of the lower lumbar spine obtained in the same patient as Fig. 1, and at the same time. The examination was considered to be normal.

Fig. 2 B. A repeat AP radiograph of the lower lumber spine in the same patient obtained 5 months later. It reveals osteoblastic metastases at sites anticipated by the earlier bone scan.

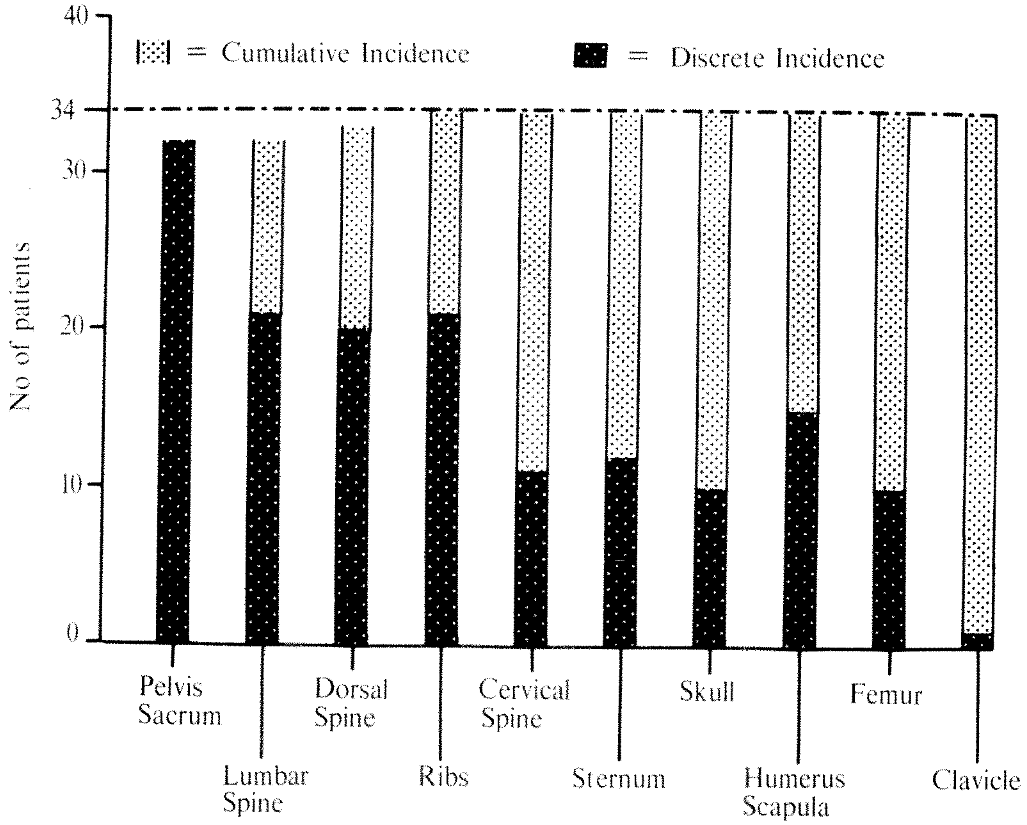

Fig. 3. Analysis of metastases by site (scan findings).

There is no *a priori* reason which makes ^{99m}Tc-P.P., or any of its technetium labelled analogues, a better bone scanning agent than its predecessors such as ^{85}Sr, ^{87m}Sr or ^{18}F. However, the relatively large dose which can be safely administered coupled with the γ emission of 140 kev., ideally suited to the physical attributes of existing detectors, provides information density which is at present unmatched.

Use of one of this new generation of bone scanning agents can thus be advocated in the context in question. Conventional radiography is not rendered obsolete, however. In our experience a limited X-ray examination of pelvis and lumbar spine, if supplemented by radiographs of scan-positive sites, is necessary to provide a base line in respect of those areas most likely to be involved in metastatic disease (Fig. 3) and to demonstrate coincidental disease. However, by thus limiting radiographic examination, as against a full skeletal survey, better diagnostic accuracy can be achieved with at least no overall increase in operating expenditure. The bone scan and limited radiographic examination utilise in total much less film than does a full metastatic survey. This difference, in our experience, more than covers the cost of the radiopharmaceutical in an institution carrying out a large number of bone scans. The professional time involved in the interpretation of the scan is certainly less than in the case of a metastatic survey and there is little difference in the technical time involved.

In addition some patients are saved from treatment which is both very costly and time consuming and which could be expected to be unsuccessful. Thus there are cogent economic arguments which support the purely clinical indications for this additional investigation.

Summary

In 100 consecutive patients with newly diagnosed carcinoma of the prostate examined by X-ray, skeletal metastases were diagnosed in 18 patients. The additional use of bone scanning with ^{99m}Tc-P.P. increased this figure to 34.

Of the 16 patients with metastatic disease demonstrated on a bone scan but not apparent at the initial reading of the radiographs, confirmatory evidence has been forthcoming in 11.

X-ray examination, which need only be of limited scope, remains desirable. It is necessary to exclude false positive bone scans due to coincidental abnormalities such as Paget's disease of bone.

We are indebted to Mrs Mary Laschowski both for assistance in carrying out this analysis, and for considerable secretarial help.

The illustrations were kindly prepared by Mr Karl Leisner and the statistical analyses carried out by Dr Michael Grace.

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Lymphography in Carcinoma of the Prostate

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Lymphography has become a routine procedure in some particular groups of urological malignancies, such as testicular tumours and carcinoma of the urinary bladder. In contrast, only a few reports on lymphographic investigations in patients with carcinoma of the prostate have been published (Ludvik and Zaunbauer, 1966; Fuchs, Davidson and Fischer, 1969; Esch and Fussek, 1970; Castellino, 1973; Castellino *et al.*, 1973; McCullough, Prout and Daly, 1973; Ray, Cassady and Bagshaw, 1973). The purpose of this paper is to evaluate the clinical use of lymphography in carcinoma of the prostate based upon a prospective study in a series of unselected patients.

Material and Methods

60 consecutive patients with histologically and/or cytologically verified carcinoma of the prostate were investigated between 1971 and 1973. The age of the subjects ranged from 52 to 81 years (mean: 66 years). Location and extent of the tumour at the time of pretreatment examination were judged by digital rectal examination. According to Flocks' classification (Flocks, 1963) the patients were clinically staged into 4 groups. In clinical stage I the malignant lesion was completely limited to the prostate and is probably occult. Stage II comprised those patients in whom rectal examination showed the lesion to be clinical and extended throughout most of the prostate. Stage III included those patients in whom rectal examination revealed extension of tumour beyond the prostatic capsule but without evidence of metastases. Stage IV patients had evidence of distant metastases regardless of the findings on rectal examination. In all cases, a histologic and/or cytological diagnosis of carcinoma of the prostate had been made.

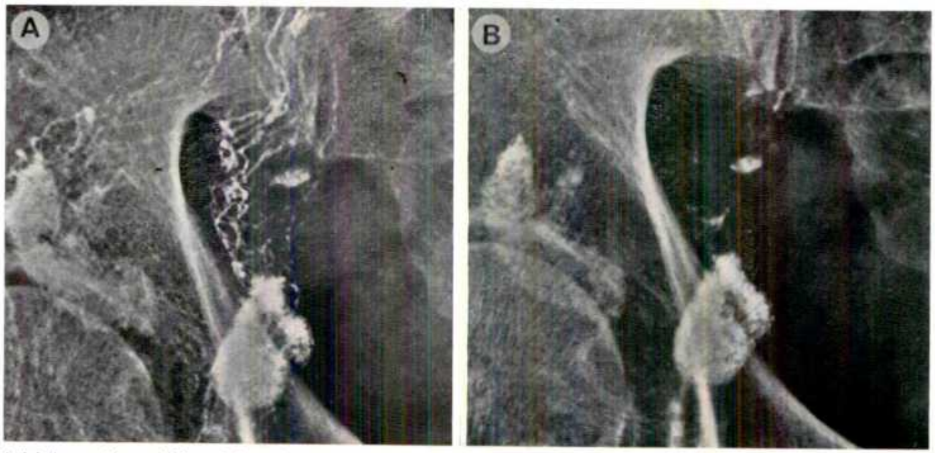
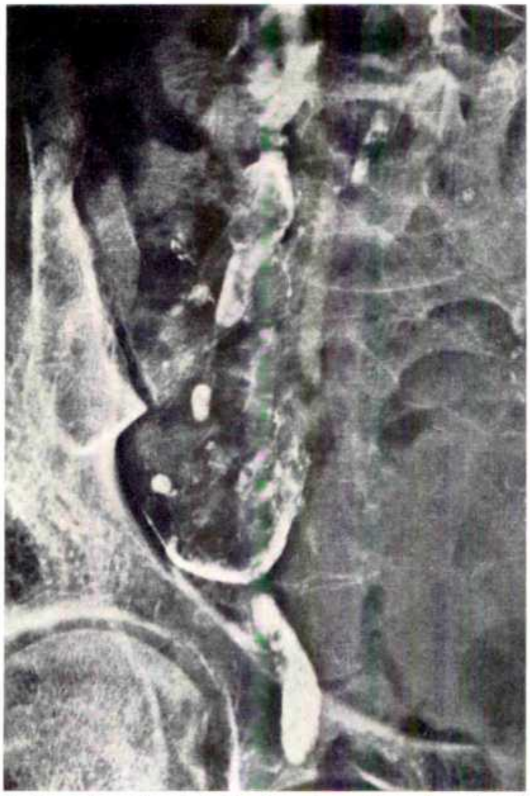


Fig. 1. Multiple confluent filling defects in two medial external iliac nodes due to malignant metastatic spread. Obliteration of intermediary sinuses. (A) Filling phase. (B) Storage phase. (68-year-old, clinical stage II.)



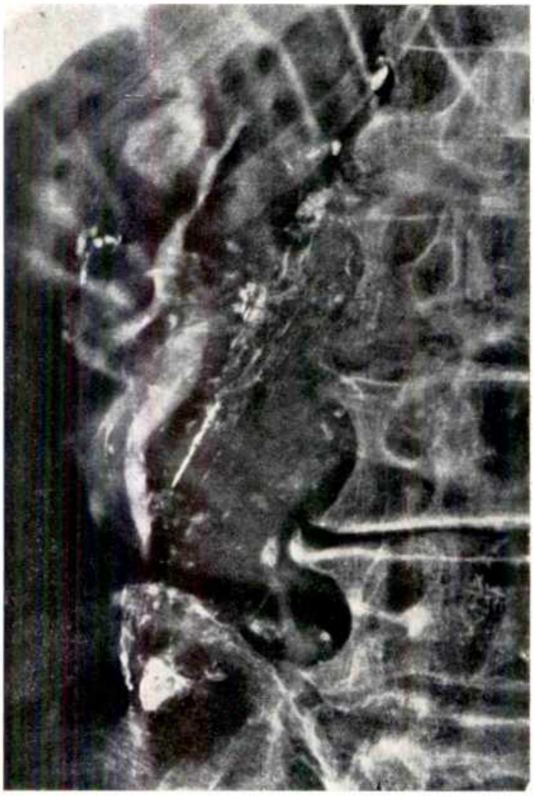


Fig. 2. Enlarged metastatic iliac external lymph nodes with large confluent central and marginal filling defects. Slight obstruction of the left ureter. (55-year-old, clinical stage II.)

Fig. 3. Extensive invasion of the aortic lymph nodes by metastatic malignant disease. Marked obstruction of the lymphatic circulation. Lateral displacement of the right ureter. (69-year-old, clinical stage III.)

All cases have been subjected to a rigorous clinical study. Serum alkaline and total acid phosphatase were measured in all patients. Radiographic examination of the chest, pelvis and spine, bilateral lymphography with inferior cavography and urography were performed in all patients. Isotope scanning of the skeleton using radioactive ^{99m}Tc was done in about a third of the cases.

Evaluation of the lymphograms was done according to strict diagnostic criteria. A positive diagnosis of malignant metastatic involvement was made only when solitary or multiple well-demarcated filling defects of at least 10 mm diameter in regional lymph nodes were present (Figs. 1 and 2). Additional obstruction of the lymphatic circulation was the other significant finding indicating malignant involvement of the lymphatic system (Fig. 3).

Results

In 31 out of 60 patients (51·6%) lymphography demonstrated malignant metastatic spread to the regional lymph nodes (Table 1). Only unilateral involvement of external iliac lymph nodes was present in 12 cases and bilateral iliac lymph node metastases in 3 cases. Metastases within aortic lymph nodes alone were observed in 3 cases. Malignant metastatic involvement of both the iliac and aortic lymph node groups was observed in 13 cases. In 10 cases pelvic venography and cavography showed abnormal findings consistent with lymph node metastases. 27 patients had abnormal urograms, but in only 9 cases were the alterations due to metastatic spread to

Table I

Cases n = 60

Positive	lymphograms	31
—	iliac lymph nodes	15
	unilateral	12
	bilateral	3
—	aortic lymph nodes	3
	unilateral	2
	bilateral	1
—	iliac+aortic lymph nodes	13
	unilateral iliac+aortic	2
	bilateral iliac+unilateral aortic	2
	unilateral iliac+bilateral aortic	1
	bilateral iliac+aortic	8

the regional lymph nodes. On digital rectal examination, 7 patients were classified as stage I, 19 patients as stage II and 34 as stage III (Table 2). In stage I there was 1 case with lymphographic findings indicating metastatic spread. The 6 negative lymphograms were proved to be correct by subsequent lymphadenectomy. 7 out of 19 patients in clinical stage II had positive lymphographic findings. Of the 34 patients classified as clinical stage III, 23 showed a pathological lymphogram due to malignant metastases.

9 out of 31 patients (29%) with lymph node metastases also presented skeletal involvement as judged radiographically and by the scintiscan (Table 2). 10 out of 29 patients (34·5%) had osteoblastic metastases in the pelvic area but normal lymphograms.

24 cases had elevated total acid phosphatase values, 19 of which (79%) had positive lymphograms. 31 patients showed abnormal values of serum alkaline phosphatase, 20 of whom (64·5%) had positive lymphographic findings. All patients with radiological skeletal involvement presented high serum alkaline phosphatase levels.

Integrating the results of rectal digital examination, lymphography, and the radiographic and isotope examinations of the bone, the final staging classification of the 60 patients was as follows: stage I: 6 cases; stage II: 8 cases; stage III: 5 cases; and stage IV: 41 cases.

Discussion

The lymphatic system is an important route for dissemination of prostatic carcinoma. The 50% rate of positive lymphograms in our case material of 60 patients clearly demonstrates this fact. The more advanced staged tumours were found to metastasise to lymph nodes more frequently. In the 26 cases of stage I and II on digital rectal examination, only 8 (30·5%) cases had positive lymphograms, whereas in the 34 patients of stage III 23 positive lymphograms (68%) were encountered. These results compare favourably with the lymphographic results of 2 other working groups (Esch and Fussek, 1970; Castellino, 1973; Castellino *et al.*, 1973; McCullough, Prout and Daly, 1973). Secondary deposits in lymph nodes are, therefore, rather common, as might be expected from the frequency of perineural lymphatic involvement (Ivker, Keesal and Leberman, 1961; Ardvino and Glucksman, 1962). Flocks (1963) reported an 8·2% frequency of lymph node involvement in 85 patients with localised carcinoma, but a 40% rate in cases of extraprostatic infiltration.

A frequency rate of abnormal radiographs and/or isotope scans of 31·6% was encountered in our case material, compared to the 51·6% frequency rate of positive lymphograms. Consequently tumour spread to the bone by the pelvic and vertebral venous system is less frequent than regional lymph node involvement.

Table II

	Digital rectal examination stages											
	Total			I			II			III		
	LN	LP	Total	LN	LP	Total	LN	LP	Total	LN	LP	Total
Lymphography	29	31	60	6	1	7	12	7	19	11	23	34
Serum alkaline phosphatase elevated	11	20	31	2*	—	2*	—	5	5	9	15	24
Total acid phosphatase elevated	5	19	24	—	—	—	1	3	4	4	16	20
Skeletal metastases (Radiograms/ Isotopes)	10	9	19	—	—	—	4	3	7	6	6	12

* 2 patients with hepatic disease.
LN = negative lymphogram.
LP = positive lymphogram.

There is no predominance of haematogenic metastatic spread to the bone in cases with positive lymphographic findings. Skeletal metastases of prostatic carcinoma occur, therefore, independently from lymphatic dissemination of the tumour.

Elevation of the total acid phosphatase suggests the simultaneous presence of regional lymph node metastases, since 79% of all cases with positive lymphograms, and only 16% with negative lymphograms, had abnormal values.

As would be expected, elevation of the serum alkaline phosphatase was not found with increased frequency in the presence of lymphogenic metastatic spread of the tumour.

The clinical value of lymphography depends upon the accuracy of its results. *The application of strict diagnostic* criteria in our case material *guarantees an accuracy rate of 85 to 90%*, as has been demonstrated in carcinoma of the uterine cervix (Fuchs and Böök-Hederström, 1961; Fuchs and Seiler-Rosenberg). These figures are similar to the 88% confirmation rate of the lymphographic findings by histology reported by Ray, Cassady and Bagshaw (1973) in 20 selected patients with apparently localised prostatic carcinoma.

Solitary or multiple well-demarcated filling defects with a minimal diameter of 10 mm in regional lymph nodes are diagnostic with obliteration of the intermediary sinuses by malignant metastatic foci (Figs. 1 and 2). Filling defects of smaller size do not have the same diagnostic quality indicating malignancy. In these cases additional signs of obstruction of the lymph circulation are necessary for a conclusive diagnosis of lymph node metastasis. Obliteration and collateral circulation are definite signs of lymphatic obstruction (Fig. 3). Delayed contrast filling of lymph vessels 24 hours following injection of contrast material, is mainly due to technical factors and must not be regarded as a sign of lymphatic obstruction. Increase of lymph node size and a globular shape of lymph nodes are unreliable signs of lymph node metastases. Dislocation of lymphatics and lymph nodes cannot be regarded as a pathognomonic sign of malignancy, since elongation of the concomitant arteries due to arteriosclerosis frequently leads to displacement of the iliac and aortic lymphatic systems. Applying these strict diagnostic criteria, the rate of false positive diagnosis is minimal. The therapist can, therefore, rely on a positive lymphographic finding and select the appropriate therapeutic treatment.

The first regional lymph nodes of the prostate, the external iliac and medial common iliac lymph nodes, are routinely demonstrated by lymphography. Only the paravesical lymph nodes which may be interspersed are not visualized by lymphography. Consequently, lymphatic metastatic spread to the regional lymph nodes may be recognised by lymphography. Small malignant metastatic foci are, however, difficult to detect because of the restricted resolution of the macroscopic method of lymphography and the great variation of lymph nodes with their physiological fibrolipomatous filling defects. A negative lymphogram does not, therefore, exclude malignant metastatic deposits in regional lymph nodes. This fact has to be considered when determining therapeutic options. However, absence of malignant involvement of regional lymph nodes, as judged by lymphography, does exclude advanced disease.

As was the case with one of our patients, the first presenting sign of prostatic cancer may occasionally be a metastatic deposit in the supraclavicular or even the axillary lymph nodes (Butler, Howe and Johnson, 1971). The carcinomatous cells reach the supraclavicular lymph nodes by way of the thoracic duct. Contrast filling of the supradiaphragmatic lymph nodes is a frequent lymphographic finding. In a study of 336 lymphograms, the supraclavicular lymph nodes were visualised in 44%; the axillary lymph nodes in 2·4% (Fuchs, Davidson and Fischer, 1969). These data explain the occurrence of malignant metastatic spread to supradiaphragmatic lymph nodes in carcinoma of the prostate.

The choice of therapeutic approach in carcinoma of the prostate is mainly determined by the presence of extracapsular extension of the neoplasma, and the metastatic involvement of the regional lymph nodes or distant dissemination to the bone. Radical prostatectomy, external beam radiography, interstitial irradiation, and hormonal therapy, or a combination, are the modes of therapy applied. In disease limited to the prostate, radical prostatectomy has been advocated, and 5-year survival rates of between 30% and 91% have been reported (Vickery and Kerr, 1963; Whitmore, 1963; Culp, 1967; Jewett *et al.*, 1968; Flocks, 1969; Gilbertsen, 1971). Once palpable extracapsular extension of the neoplasm has occurred, the success of this operation is limited, due to the significant local recurrence rate and the high incidence of pelvic lymph node involvement (Whitmore 1963,; Jewett *et al.*, 1968). Laparotomy in patients with localised carcinoma has, therefore, been advocated by some authors (Castellino,1973; Castellino *et al.*, 1973; McCullough *et al.*, 1973; Ray *et al.*, 1973) to evaluate malignant metastatic spread to the regional lymph nodes. The relatively high accuracy of lymphographic interpretation of 85% and, in particular, the very low rate of a possible false positive diagnosis, seems to make this aggressive diagnostic approach unnecessary. Negative lymphographic findings in the clinical stages I and II preclude advanced malignant disease and radical prostatectomy, including lymphadenectomy, would, therefore, seem to be justified. In the presence of lymph node metastases on the lymphogram and in clinical stages III and IV, external megavoltage radiotherapy and/or hormone therapy—including orchidectomy—are the alternative methods of choice. The anatomy of the iliac and aortic lymph nodes is well displayed on the lymphograms, and the irradiation of the iliac and aortic portal fields may be planned accordingly.

Summary

60 patients with carcinoma of the prostate of all clinical stages were investigated by lymphography.

Positive lymphographic findings were present in about 50% of the cases.

The more advanced tumours were found to metastasise more frequently.

Lymphography is indispensable to select patients with clinically limited disease to the prostate for radical prostatectomy.

The anatomical display of the iliac and aortic lymph nodes on the lymphogram facilitates the selection of the portal fields in external beam megavoltage radiotherapy.

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.Adrenal Suppression in the Treatment of Carcinoma of the Prostate

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The treatment of oestrogen resistant prostatic carcinoma by further interference with endocrine balance, either by adrenalectomy or hypophysectomy is well recognised (Maddy, Winternitz and Norrell, 1971; Murphy *et al.*, 1971). However, hypophysectomy and adrenalectomy are major surgical undertakings with appreciable mortality and morbidity and while pituitary irradiation is an effective safe procedure (Fergusson and Hendry, 1971) it is not entirely without complications and we have therefore sought a method of securing a "medical adrenalectomy" in the management of prostatic cancer.

Aminoglutethimide, a derivative of glutarimide, was introduced in the United States in 1960 as an anticonvulsant, but was subsequently withdrawn as a result of reports of severe endocrine disturbance resulting from its use (Rallison, Kumagai and Tyler, 1967; Camacho *et al.*, 1967). Further investigation indicated that aminoglutethimide inhibits adrenal production of aldosterone, cortisol, and androgens (Dexter *et al.*, 1967) probably by interfering with the conversion of cholesterol to delta 5-pregnenolone (Cash *et al.*, 1967). There is no evidence to indicate that it inhibits testicular function (Gaunt, Steinetz and Chart, 1968). It was therefore suggested that aminoglutethimide might be of use in the management of hormone dependent tumours (Hughes and Burley, 1970), and a recent report has indicated that aminoglutethimide has a limited role in the management of advanced breast cancer (Griffiths *et al.*, 1973).

Since 1970, aminoglutethimide has been employed in the management of certain cases in the Prostatic Carcinoma Unit of the Institute of Urology and this paper presents our experience in its use in the treatment of prostatic cancer.

Patients and Methods

Patients

26 patients with carcinoma of the prostate were studied, with an average age of 64·3 years (range 48 to 77 years).

The diagnosis was established in each case by histological or cytological examination of a prostatic biopsy.

The extent of the disease was assessed by serum acid and alkaline phosphatase estimation, intravenous urography and chest X-ray, skeletal surveys by both X-ray and 87 m Sr bone scintigraphy, and cystoscopy and examination under anaesthetic. 20 patients (77 %) had bone metastases, of whom 17 (67 %) complained of bone pain: 6 patients (23 %) had no evidence of metastatic disease.

Methods

Aminoglutethimide was administered orally in divided daily doses of 500 mg to 1 g, in conjunction with stilboestrol 1 mg thrice daily. In all except 4 cases replacement steroid therapy with cortisone 25 to 50 mg daily and fludrocortisone 0·1 mg daily was started simultaneously with the aminoglutethimide: in the remaining 4, replacement steroid therapy was started after an interval of 1 to 2 weeks. In 6 patients (23%) aminoglutethimide and stilboestrol were used as the primary treatment of the carcinoma: in the remaining 20 (77%) aminoglutethimide was employed only after failure to respond to oestrogen, or relapse while on oestrogen. No patient received aminoglutethimide without oestrogen.

Results were assessed subjectively by pain relief or resolution of urinary symptoms, and objectively by serial serum acid phosphatase estimation, assessment of prostatic size by rectal examination, and serial X-ray and radioisotope skeletal surveys.

In the 4 patients not receiving replacement steroid therapy plasma cortisol levels were estimated fluorimetrically after dichloromethane extraction (Mattingly, 1962) and in 11 patients plasma testosterone levels were estimated by radioimmunoassay (Collins *et al.*, 1972).

Results

Symptomatic Response

The subjective response to treatment is shown in Table I. The patients were divided into 3 groups as follows:

Group 1: Complete response: Abolition of pain or complete remission of urinary symptoms.
Group 2: Partial response: Some pain relief or incomplete resolution of urinary symptoms.
Group 3: No response: no symptomatic difference before and after treatment.

Of the 8 patients in Group 1, 5 were given aminoglutethimide as primary treatment, and 3 received aminoglutethimide only after failure of conventional oestrogen therapy. Nine patients showed no response to aminoglutethimide, of whom only 1 received the drug as his primary treatment.

Table I

Symptomatic Response to Aminoglutethimide

		Response to Aminoglutethimide		
		Group 1 Complete	Group 2 Partial	Group 3 None
Non-metastatic	6 (23%)	4 (15%)	0	2 (8%)
Metastatic	20 (77%)	4 (15%)	9 (35%)	7 (27%)
Total	26	8 (30%)	9 (35%)	9 (35%)

Overall, 13 of the 20 patients with metastatic disease fell into groups 1 and 2; of the 17 patients with bone pain 10 (59%) had complete or partial relief of pain. 12 of 20 patients (60%) given aminoglutethimide after failure of oestrogens showed some symptomatic improvement.

Objective Response

Six patients showed evidence of tumour regression. 13 patients had elevated serum acid phosphatase before aminoglutethimide treatment, and in 4 of these (31%) the acid phosphatase level subsequently became normal. In 2 of these patients there was no other sign of objective response, 1 showed decreased activity of bone metastases and in 1 the tumour diminished in size as assessed rectally. One patient with a normal acid phosphatase showed decreased bone activity, and 1 patient showed resolution of ureteric obstruction on intravenous urography. Of the 6 patients with objective evidence of response, 5 were given aminoglutethimide as primary treatment.

Duration of Response

Of the 17 patients with some symptomatic response, 5 were given relief until death, for periods of up to 8 months, 5 who are still alive have been given relief which has persisted until the present, after periods ranging from 8 months to 2 years, and the remaining 7 were given only transient relief for an average period of 3·5 months (range 3 weeks to 10 months).

Survival

Nine patients are still alive, 4 to 33 months after starting aminoglutethimide. The remaining 17 patients are all dead, having survived an average period of 8 months after starting aminoglutethimide (range 1 to 20 months).

Plasma Cortisol

We were unable to demonstrate any fall in plasma cortisol in the 4 patients tested. We feel that this failure is due to interference with the method of measuring cortisol, either by oestrogen or by aminoglutethimide itself.

Plasma Testosterone

We have found that stilboestrol in a dose of 1 mg 3 times daily produces complete suppression of testicular production of testosterone (Shearer *et al.*, 1973). No further fall in circulating testosterone after administration of aminoglutethimide was noted in the 11 patients tested.

Side-effects

These are numerous and are shown in Table II. Only 7 patients (27%) were completely free of side-effects, and in 8 (31%) side-effects were sufficiently severe to require cessation of treatment.

Table II

Side effects of Aminoglutethimide

Side-effects	Number of Patients Affected
Hypotension	4 (15%)
Nausea and vomiting	8 (30%)
Lassitude	11 (42%)
Depression	5 (19%)
Oedema	3 (11·5%)
Skin rash	1 (4%)

12 patients (46%) suffered from 2 or more side-effects. The commonest side-effect was a non-specific personality change, best described as extreme lassitude, but the 5 patients with depression were suicidally depressed and treatment had to be discontinued. Three of the 4 patients with hypotension were those not receiving replacement steroids and in 2 of these the hypotension amounted to an Addisonian crisis. The 4th patient with hypotension presented as an emergency with an Addisonian crisis secondary to intercurrent infection. In all cases the hypotension responded rapidly to commencing or increasing replacement steroids.

Comparison with Pituitary Irradiation

Seven of the patients in this series were treated by pituitary irradiation for severe bone pain after failure of aminoglutethimide: 5 of these patients subsequently gained symptomatic relief, although the effect of pituitary irradiation tended to be delayed in these patients for up to 3 weeks, whereas in patients undergoing pituitary irradiation without previous aminoglutethimide, response is usually almost immediate. It was noticeable that the patients' feeling of general well-being was much greater after pituitary irradiation than while they were on aminoglutethimide.

Discussion

The value of oestrogens in the management of prostatic carcinoma has been well recognised for over 30 years (Huggins and Hodges, 1941; Fergusson and Franks, 1953) but a proportion of cases do not respond to oestrogen therapy, and a further group, after an initial response, "escape" from hormonal control. In view of the acknowledged dependence of prostatic cancer on an available supply of testosterone, it has been postulated either that these oestrogen-resistant tumours are no longer hormone-dependent, that they are able to utilise for their metabolism the very small circulating amounts of testosterone still available, or that compensatory mechanisms have provided an alternative hormonal source (Farnsworth, 1970). On theoretical grounds, therefore, it is possible that suppression of adrenal activity might lead to tumour regression by reducing adrenal androgen production and this supposition is strengthened by the proven success of pituitary ablation in this field. Our finding that pituitary irradiation (Shearer *et al.*, 1973) is followed by a fall in plasma testosterone beyond that achieved by oestrogens alone tends to confirm this view, but it is surprising that in spite of the success of aminoglutethimide in the palliation of 60% of our hormone-resistant tumours, we have been unable to demonstrate a similar fall. This finding is in contrast to our earlier experience using a different method of measuring plasma testosterone but it casts doubt on the postulated mode of action of aminoglutethimide and suggests that it is effective not by testosterone suppression but by a non-specific alteration in the hormonal environment interfering with tumour metabolism, or by direct action on the tumour.

The best response to aminoglutethimide was achieved when it was used, in conjunction with oestrogens, as primary treatment, but the number of patients is small (5 responders out of 6 treated) and it is likely that a similar response could have been achieved with oestrogen alone. A larger series of patients followed for a long time would be needed to settle this point, but we feel that such a study would not be feasible in view of the high incidence of serious side-effects we have found in the use of aminoglutethimide.

Conclusions

We feel that aminoglutethimide has a limited role to play in the palliation of oestrogen-resistant carcinoma of the prostate, but for the reasons discussed above it is not suitable as a first-line treatment. There is no evidence that the progress of the disease is arrested by aminoglutethimide, and it is inferior both in extent and duration of response to pituitary irradiation. Failure to respond to aminoglutethimide does not however preclude a subsequent satisfactory response to pituitary ablation.

Summary

Experience of 26 patients with carcinoma of the prostate treated by adrenal suppression with aminoglutethimide is reviewed. 60% of hormone resistant tumours showed some response.

A fall in plasma testosterone beyond that achieved by oestrogens was not observed.

A high incidence of side-effects was noted.

A limited role for aminoglutethimide in the management of prostatic carcinoma is suggested.

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Fine Structural Changes in Rat Prostate 5 Months After the Experimental Introduction of 20-Methylcholanthrene

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The introduction of the carcinogen 20-methylcholanthrene into the dorsolateral and ventral lobes of the rat prostate causes histological changes in the acinar epithelium which range from slight hyperplasia to squamous cell carcinoma (Dunning, Curtis and Segaloff, 1946; Lasnitzki, 1950, 1969; Allen, 1953; Mirand and Staubitz, 1956; Hirai *et al.*, 1969). Lasnitzki (1951, 1970) has described early changes in the fine structure of the mouse and rat prostate cultured in medium to which 20-methylcholanthrene has been added.

Little attention has been paid to the ultrastructure of the changes induced by 20-methylcholanthrene in the ventral and dorsolateral lobes of the rat prostate in vivo. The present series of experiments were designed to study these changes.

Material and Methods

Material

53 young male Wistar rats (60 to 70 gm in weight) fed on standard laboratory chow were used.

Surgical procedure

General anaesthesia was induced by ether and maintained by fluothane and oxygen. A small vertical midline incision was made after shaving the lower abdominal wall. The incision was carried to the root of the penis and the bladder and prostate exposed by separating the abdominal muscles. The ventral lobes of the prostate are immediately available for injection, 22 animals were injected with 20-methylcholanthrene into the left ventral lobe of the prostate.

To expose the left dorsolateral lobe, the bladder is grasped by non-toothed dissecting forceps, freed from any fibrous adhesions and pulled to the right of the midline. If the dorsolateral lobe is not sufficiently visualised by this manoeuvre the left vas deferens is ligated and divided between stay sutures as close to the prostate as possible. This allows adequate exposure of the dorsolateral lobe for injection purposes (0·1 ml of 3% 20-methylcholanthrene in aqueous suspension). 31 animals were injected in the left dorsolateral lobe. After replacing the bladder and prostate the wound is closed by suturing the recti and sheath as one layer and the skin and subcutaneous tissues as a second layer. If care is taken to tie the knots of the skin sutures so as to clearly evert the skin edges there is little chance that the animal will gnaw at the sutures and wound healing should be by first intention.

Electron microscopy

1 mm cubes of tissue from both right and left prostatic lobes were fixed in cold buffered isotonic paraformaldehyde (Peters and Palay, 1966) post-osmicated in 1% cold buffered osmium tetroxide, dehydrated in acetone and embedded in epon (Luft, 1961). Thick sections (1 to 2 μ) were cut and stained with toluidine blue-pyronin (Ito and Winchester, 1963) and the block trimmed; thin sections were cut on an L.K.B. ultramicrotome, stained with uranyl acetate and viewed on a Hitachi HS8 at 50 KV. Electron micrographs were taken at 4,000 to 19,000 and enlarged photographically. Cryostat sections (40 μ) were processed in Gomori's acid phosphatase medium (Holt and Hicks, 1961) then fixed in 1% cold buffered isotonic osmium tetroxide, processed and embedded in epon as described. The ultra thin sections were first examined unstained, then stained with uranyl acetate.

All tissues were taken from frank tumour or near foci of 20-methylcholanthrene on the left side; control tissue was taken from the right side.

Results

The rats were killed when it was obvious that a tumour had arisen or at 5 to 6 months post operation. This latter date was chosen because in a few animals which did not show an overt

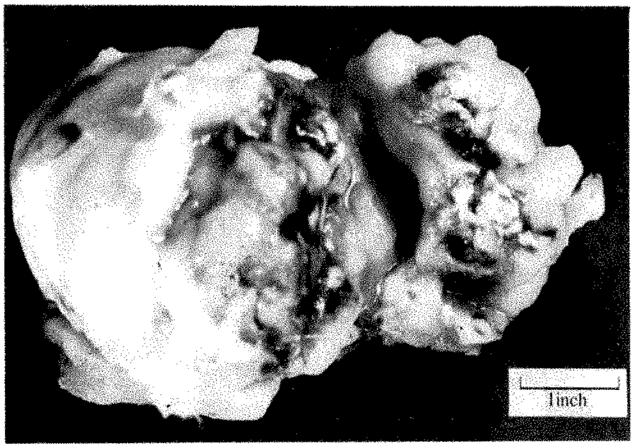

Fig. 1. Illustrates the general appeareance of the gross tumour in a well-developed squamous cell carcinoma 6 months after the injection of 20-methylcholanthrene.

tumour on abdominal examination it was found that tumours had occurred in the dorsolateral lobe.

On inspection of the animals most tumours extended into and involved the abdominal muscles. With few exceptions the tumours tended not to produce obstructive complications and because of this animals have to be inspected weekly to avoid missing early lesions. Wound hernia occurred in less than 5% of animals and is easily recognised on palpation.

Gross anatomy

The left ventral and dorsolateral lobes showed evidence of tumour development on gross examination in 20 rats. In 14 rats there was no gross tumour but residual 20-methylcholanthrene could be recognised at the site of injection. Tumours rarely involved the non-injected lobes of the right prostate. In 8 rats with gross tumours (Fig. 1) metastases had occurred with transperitoneal spread to the undersurface of the diaphragm, to the liver and abdominal viscera.

Light microscopy

The histological changes seen in the injected left ventral and left dorsolateral lobes of the prostate are summarised here (Table).

1. In areas not involved in the tumour process, and apparently unaffected by the carcinogen, the columnar cells are indistinguishable from normal cells.
2. Affected acini may be lined by simple cuboidal or squamous epithelium, and an increase in the circumacinar connective tissue is apparent.
3. Hyperplastic acini are seen in areas surrounding overt tumours or approximating deposits of 20-methylcholanthrene, the acinar wall is often folded, and tall columnar cells almost obliterate the lumen.
4. Neoplastic change is typified by small groups of cells becoming stratified; some superficial cells are found free in the lumen often with small eosinophilic masses lying between them, with a local infiltration of leukocytes and round cells. The final stage is represented by the development of the typical epithelial pearls of squamous cell carcinoma. Tumour growth is very rapid, and the normal architecture of the gland is completely obliterated.

Electron microscopy

The areas of cellular change described in the histology section are identified on the toluidine blue 1μ section, and the block trimmed to present this area for fine sections.

Table

Histological changes in the rat prostate parenchyma following the introduction of 20-methylcholanthrene

		Histological appearance
Normal Acinus ↘ ↓ Tall columnar epithelium with a supranuclear clear zone	20-methylcholanthrene →	1. Normal columnar epithelium ↓ 2. Hypertrophied epithelium ↓ 3. Basal cell proliferation and increased periacinar connective tissue ↓ 4. Sloughing of hypertrophied cells into the acinar lumen ↓ 5. Stratification of the epithelium from the basal cells ↓ 6. Keratinisation ↓ 7. Squamous cell carcinoma

1. Acini in areas apparently unaffected by the 20-methylcholanthrene show two types of lining epithelium
   (*a*) normal cells as described for healthy adult rat prostate
   (*b*) columnar cells with an irregular luminal edge, caused by projection of the apical zone beyond the confines of the junctional complex giving the cell a dentate appearance; there are no microvilli (Fig. 2). The cisternae of the rough endoplasmic reticulum (R.E.R.) are dilated and filled with a rather dense granular substance and the apical cisternae in some cells open directly into the lumen. The mitochondria often show cloudy swelling with a few cristae projecting into an electron lucent interior. The Golgi apparatus and associated smooth membranes appear to be more extensive. Lysosomes are a particular feature of these cells and form large masses with contained myelin figures and altered mitochondria; acid phosphatase is present (Fig. 3). The basally placed nucleus is often irregular in outline with deep clefts which destroy the normal rounded appearance, a large nucleolus and, commonly, clumping of the chromatin. Fat globules are often present in the infranuclear zone. The R.E.R. may be reduced here and free ribosomes increased.

   Not all the cells in a particular acinus will show these changes in fine structure, and such minimal signs as a few altered mitochondria and small myelin figures may be the only evidence present.
2. In the cuboidal or squamous cell there may be a reduction in the number of microvilli, the R.E.R. is markedly reduced, and large numbers of polysomes are seen in the electron lucent cytosome. A few mitochondria are found throughout the cytosome commonly showing evidence of cloudy swelling. Lysosomes are present. The round or irregular nucleus is basally placed, hyperchromatic, with a well-defined nucleolus, suggestive of impending mitosis (Fig. 4).

   Some of these acini are lined by undifferentiated cells with distended electron lucent microvillous processes often with contained myelin figures. There is no R.E.R., some smooth membranes, free polysomes and in one instance massive numbers of mitochondria showing cloudy swelling. Cell outlines are difficult to appreciate and the nuclei are haphazardly arranged. The basal lamina is absent from some areas and only amorphous ground substance separates smooth muscle fibres from the epithelium.

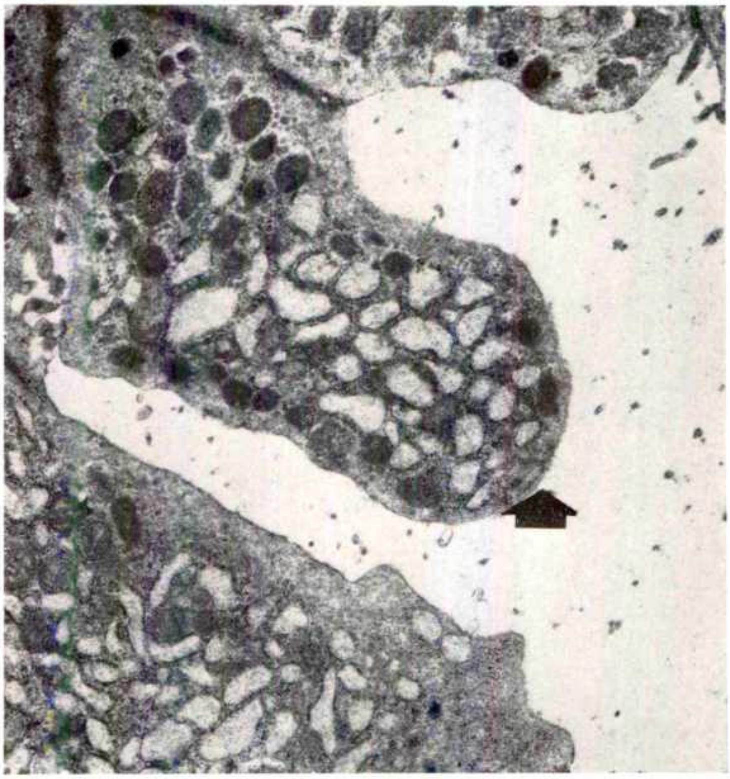

Fig. 2. Rat ventral prostate, 5 months after the injection of 29-methylcholanthrene. Illustrates the apical projections (arrowed) of the hyperplastic cell. Uranyl acetate. × 10,500.

3. The fine structure of the hyperplastic cell is an exaggeration of the normal healthy prostatic acinar cell.
4. The stratified epithelium seen preliminary to the squamous cell carcinoma has the following characteristics: The basal cells are undifferentiated and only rarely show properties in common with the secretory cell. Some R.E.R., free polysomes and altered mitochondria are present in the cytosome, with smooth membranes of the Golgi. The nuclei are irregular and hyperchromatic. The cells nearer the lumen contain electron dense granules, these latter are also present between the cells and in the acinar lumen. Lysosomes are commonly present and the basal lamina is interrupted. The stratified epithelium typical of the squamous cell carcinoma is shown in Fig. 6. Tonofibrils are a feature of the cells.

The frank tumours classified histologically as fibrosarcomata, or rhabdomyosarcomata showed no prostatic secretory tissue and are not described here.

Discussion

The carcinogen methylcholanthrene has been used in studies of the changes in prostatic epithelium associated with tumour formation both in vivo (Allen, 1953; Mirand *et al.*, 1956) and in tissue culture (Lasnitzki, 1950, 1964, 1965, 1969 and 1970). Prostatic parenchymal tumours induced by this agent have been squamous cell carcinomas (Dunning *et al.*, 1946; Allen, 1953) which first became evident 100 to 200 days following the introduction of the carcinogen directly into the gland.

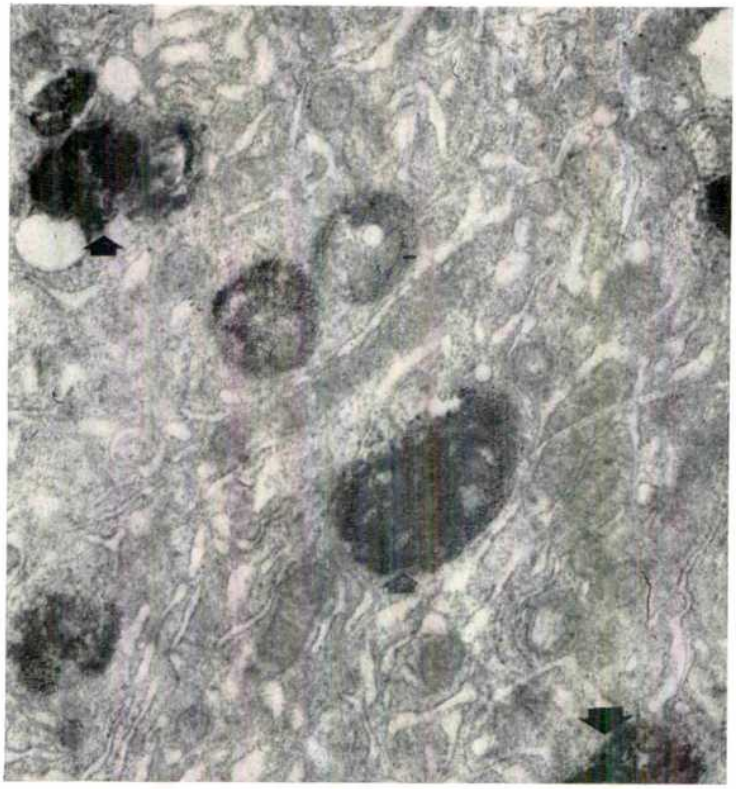

Fig. 3. Rat dorsolateral prostate, 5 months after the injection of 20-methylcholanthrene. Illustrates the local acid phosphatase reaction of the dense bodies and myelin figures (arrowed). Uranyl acetate. × 15,000.

The histological changes described in affected ventral and dorsolateral prostatic acini suggest an initial hypertrophy of the epithelium, followed by desquamation of these cells and subsequent replacement by basal residual cells. Proliferation of these basal cells results in the progressive development of a stratified epithelium, a stratified squamous epithelium and the heavily keratinised epithelium characteristic of squamous cell carcinoma. The increase in circumacinar connective tissue, and leucocytic infiltration shows a response to the irritant carcinogen.

The ultrastructural studies have shown that even in areas apparently unaffected by the methylcholanthrene some change could be distinguished in the individual cells. Brandes (1966) described the normal prostatic cell with an extensive rough endoplasmic reticulum, a prominent Golgi apparatus, numerous small dense mitochondria and a regular basal nucleus.

Apart from these normal cells we were able to demonstrate cells which were markedly increased in height and bulged into the lumen. The latter feature could be associated causally with the disappearance of microvilli and perhaps caused by dilatation of the endoplasmic reticulum; in addition the Golgi complex was markedly expanded. These changes suggest increased cellular activity, but the degenerative changes in the mitochondria which have few cristae and exhibit cloudy swelling, together with an increase in secondary lysosomes suggest that the process is temporary and in these cells may have passed its peak. Interestingly, these changes are identical with those noted following castration (Brandes, 1966) and perhaps reflect the preliminary influence of the carcinogen on the androgen control of the cell. Further, the modification of the mitochondria, irregularity of nuclear outline and accumulation of fat in the basal cytoplasm of these hypertrophied cells are recognised as precancerous (Oberling and Bernhard, 1961; Le Breton and Moulé, 1961).

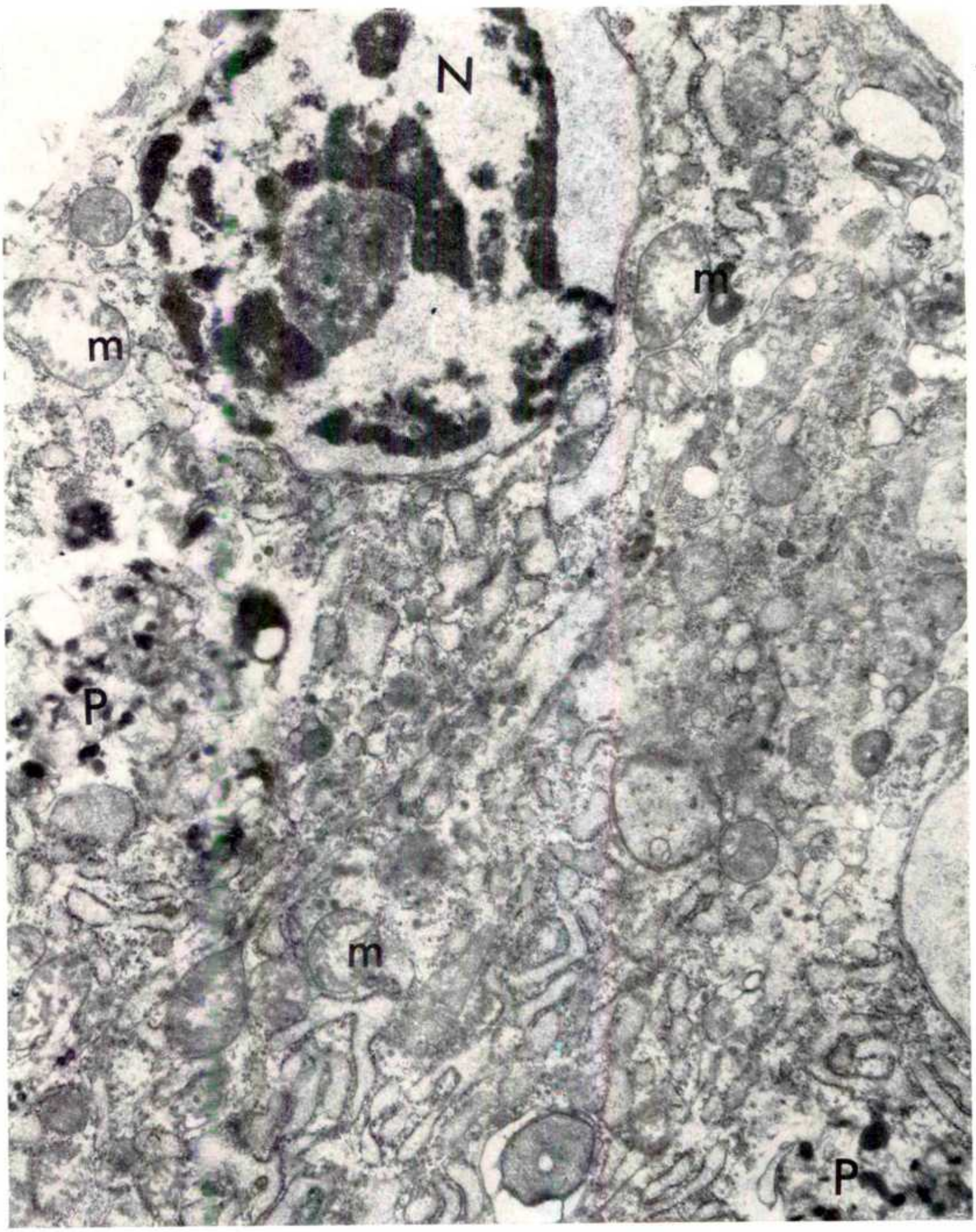

Fig. 4. Rat dorsolateral prostate, 5 months after the injection of 20-methylcholanthrene. Illustrates mitochondria showing degenerative change (M), large phagosomal masses (P), and a hyperchromatic nuclues (N) in the more flattened type of epithelium, becoming stratified. Uranyl acetate. × 10,500.

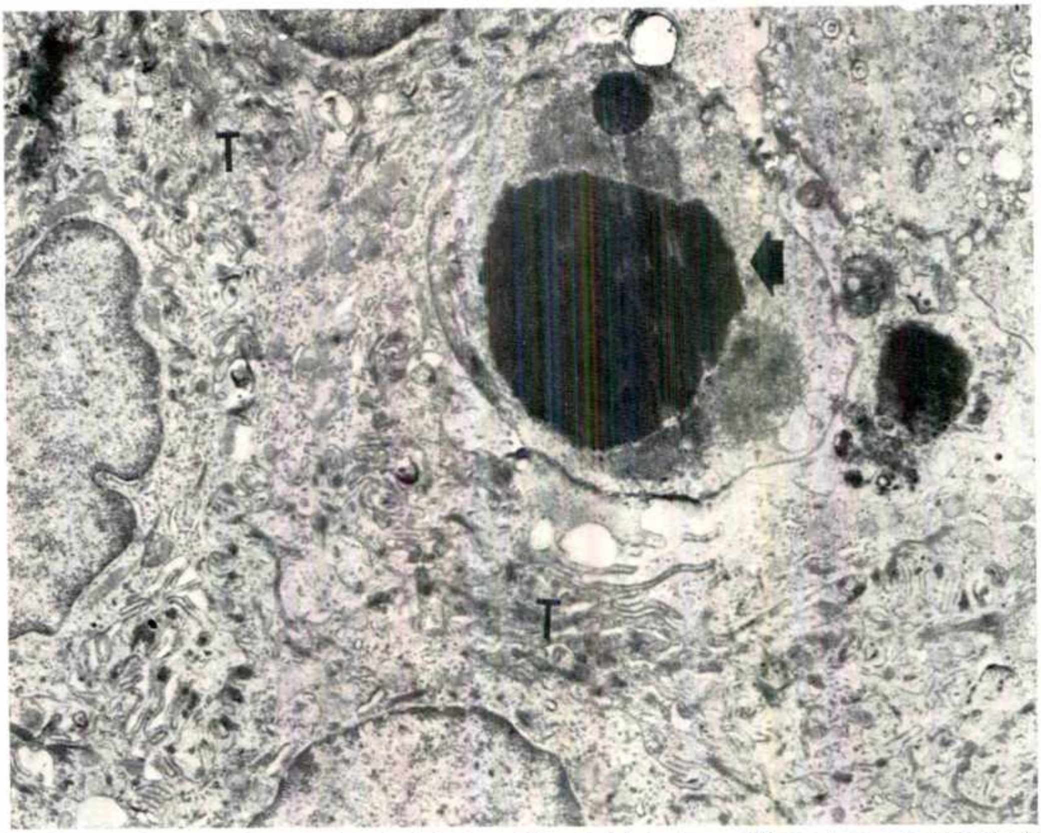

Fig. 5. Rat ventral prostate, 6 months after the injection of 20-methylcholanthrene. This is a low power electron micrograph through an "epithelial pearl" showing a dense mass of keratin (arrowed) and the keratinising epithelial cells with their typical tonofibrils (T). Uranyl acetate. × 5,000.

Lasnitzki (1964) showed that "hyperplastic" cells occur in tissue cultures of ventral prostate within five days of exposure to methylcholanthrene. The same author (Lasnitzki, 1969) reported that 20-methylcholanthrene introduced into the culture medium induced hyperplasia of rat ventral prostate epithelium, a proliferation of reserve cells, increased protein production temporarily by the hyperplastic cell with eventual shedding of the latter into the acinar lumen.

In areas where a reduction in epithelial height is seen, there is evidence of diminished secretory activity with a reduction in the volume of R.E.R., and of Golgi vesicles and an increase in mitochondrial degeneration and in the number of lysosomes. At the same time there is an increase in the number of free polysomes. These changes suggest some dedifferentiation of the cell, and it is possible that these represent uncommitted basal reserve cells and therefore comparatively undifferentiated. The appearance of these undifferentiated basal cells in the stratified epithelium prior to keratinisation suggest that this dedifferentiation is a preliminary to proliferative change; the accumulation of tonofibrils in the more superficial cells is an indication of subsequent keratinisation and the establishment of an easily identifiable squamous cell carcinoma.

In conclusion, the well-defined histological changes seen in the inception of squamous cell carcinoma of the prostate have been examined with the electron microscope and a pattern of parenchymal hyperplasia, with cell death and replacement by reserve undifferentiated cells has been established. Consequent proliferation of these cells under the influence of the carcinogen leads to the development of a squamous cell carcinoma.

Summary

The fine structure of hypertrophied cells in rat prostate parenchyma after exposure to 20-methylcholanthrene is described, and some features such as degenerating mitochondria, increase in smooth membranes and lysosomes suggest that these cells are passed their peak. This is supported by the sloughing of these cells and their consequent replacement by a stratified epithelium originating in the basal undifferentiated reserve cells.

Keratinisation of the epithelium with the presence of typical tonofibrils is regarded as evidence of a fully-developed squamous cell carcinoma.

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Malignant Lymphoma of the Testis in Indians

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Malignant lymphoma presenting as a testicular tumour is rare, although frequent microscopic testicular involvement in leukaemia and generalised lymphosarcoma has been encountered at autopsies (Givler, 1969). Testicular swelling may be the first manifestation of a generalised lymphoma or the forerunner of a disseminated lymphoma. At times evidence of malignant lymphoma may be already present or appear with the testicular tumour. Solitary lymphomas of the testis have been reported, but the number is small as the disease rarely remains localised and in the majority of patients dissemination occurs within months. It is not possible to predict from the histological appearance the behaviour of a lymphoma primarily occurring in the testis.

Material and Method

In this presentation we have reviewed orchidectomy specimens and histopathologic sections of 17 patients studied in the laboratories of the Tata Memorial Hospital during the years 1941 through 1972. Sections were stained with hematoxylin and eosin. Corresponding sections were also stained for reticulin fibres by Gomori's silver impregnation method. Clinical records of all cases were critically studied for associated lesions and for follow-up data. The cases were divided into 3 groups as follows:

Group I: Testicular tumour as the only manifestation of lymphoma.
Group II: Testicular tumour followed by disseminated lymphoma during the course of the disease.
Group III: Testicular tumour following generalised lymphoma.

Clinical Features

Group I

Testicular swelling was the only manifestation in 3 cases. One of these patients was a child 5 years old and the other 2 patients were 43 years and 68 years of age respectively. One of the patients had suffered from filariasis 10 years previously and had a testicular swelling of 3 months duration. A history of hydrocele 20 years before was given by another patient. The later patient died 6 months after surgery, from a cause not relevant to the disease. There was however no autopsy. The other 2 were followed for 6 months and 5 years and 6 months after orchidectomy when they were found to be free from the disease.

Group II

12 patients presented with painless testicular swelling of 2 weeks to 6 years' duration. In 2 patients bilateral involvement of testes was present. The clinical history revealed that in 7 patients generalised lymphadenopathy occurred during the course of the disease. Abdominal lymph nodes were palpable in 8 patients with ascites in 2. Cutaneous nodules were present in 3 patients and were histologically proved to be malignant lymphoma. Involvement of the maxillary antrum occurred in 3 patients and osteolytic bone lesions in tibia, fibula and skull were noted in 1 patient each during the course of the disease. Follow-up data was available in 7 cases; all of them died within 6 months to a year after orchidectomy.

Group III

Testicular swelling had followed generalised lymphadenopathy in 2 patients. One of them had abdominal masses with ascites. Bilateral testicular involvement with a hydrocele was present in 1 patient. One of the 2 patients died within 6 months after operation.

Of 17 cases, the right testis was involved in 5 cases, the left testis in 9 cases; bilateral involvement was noted in 3 patients.

Examination of the peripheral blood did not show any evidence of leukaemia.

Postoperative radiotherapy was given to 9 patients. In 6 patients operation was followed by chemotherapy only and in 2, postoperative radiation was followed by chemotherapy.

Age Incidence

Of 17 patients the youngest was a 5-year-old child; the oldest patient was 68 years of age. The maximum number (14) of patients was between the ages of 40 years and 68 years. Eight patients were more than 50 years of age.

Pathology

Gross Findings

Ten orchidectomy specimens were available for detailed study while in 7 patients paraffin blocks and slides were sent to us from outside city hospitals. The testicular tumours varied in size from 2·2 × 2 cm to 13·5 × 9 cm. A portion of the spermatic cord was present in all the specimens. A hydrocele was present in 3 cases. Tumour had replaced the whole of the testicular parenchyma in 8 (Fig. 1) and only in 2 specimens testicular parenchyma could be identified on naked eye examination. The tumour was soft in consistency and showed a grey tan homogeneous appearance

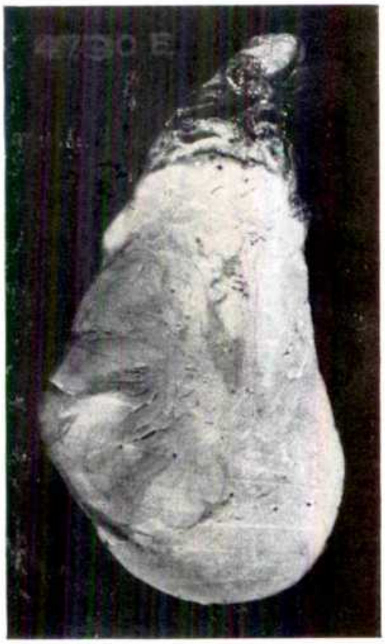

Fig. 1. Shows cut surface of orchidectomy specimen of malignant lymphoma from a 42-year-old male. Entire testicular parenchyma and epididymis are replaced by tumour.

Irregular yellowish areas of necrosis and scattered areas of cystic degeneration were present in 5 specimens. In none of the specimens had the tumour broken through tunica albuginea and tunica vaginalis. The epididymis was involved in all specimens. The cut edge of the spermatic cord showed tumour infiltration in 3 cases.

Microscopic Findings

In sections from all the tumours, cells were seen diffusely infiltrating in between and widely separating the seminiferous tubules (Fig. 2). The seminiferous tubules did not show any evidence of spermatogenesis and contained Sertoli cells with vacuolated cytoplasm. In some cases a few tubules were invaded by lymphoma cells. The adjoining testicular parenchyma did not show any evidence of intratubular involvement. Silver impregnation for reticulin showed an open network of concentric peritubular reticulin fibrils resulting from the infiltration of peritubular connective tissue by lymphoma cells (Fig. 3). This is of help in differentiating lymphoma from seminoma in which the reticulin fibres are compressed around the tubules.

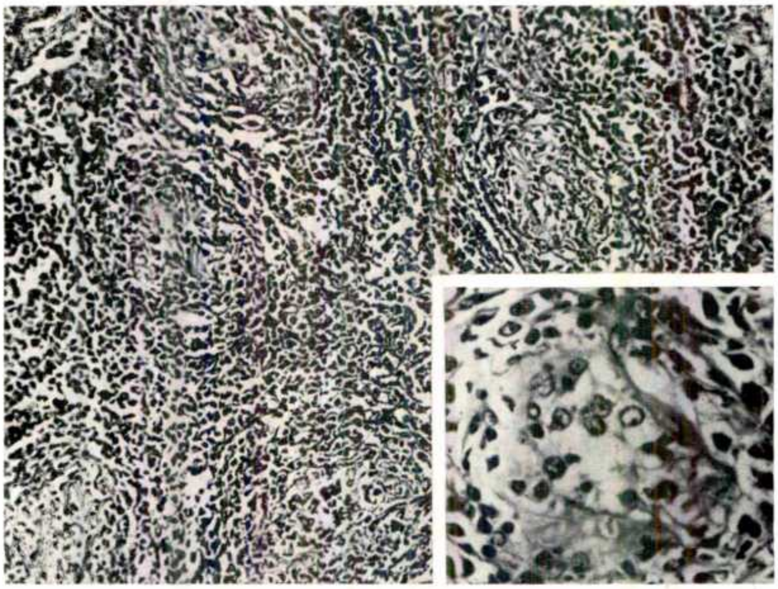

Fig. 2. Photomicrograph showing diffusely infiltrating tumour cells in between the atrophic seminiferous tubules. Inset shows atrophic seminiferous tubule containing vacuolated Sertoli cells. H & E. × 90 and × 280. (Path. no. 8392-E.)

Of 17 tumours only 3 tumours were composed of well differentiated lymphocytic cells and in 2 mixed pictures of lymphoblastic and well differentiated lymphocytic type was seen. Sections from 8 tumours revealed poorly differentiated cells of lymphocytic series. Diffuse sheets of pleomorphic cells were seen. The nuclei were round to ovoid and showed marked chromatin stippling. Mitotic figures were seen in fair numbers. These were lymphosarcomas of lymphoblastic type.

Reticulum cell sarcoma was diagnosed in 2 cases (Fig. 4). The cells showed ill-defined cytoplasmic outlines and varied in size and shape. The nuclei appeared large, vesicular and contained one or more nucleoli. Identations of nuclei (reniform) and multi-nucleated cells were also present. Fairly abundant reticulin fibrils were seen on silver impregnation. In some areas even pericellular network was seen.

Sections from 2 cases revealed Hodgkin's disease with pleomorphic picture consisting of lymphocytes, plasma cells, polymorphonuclear cells and mononuclear and multinuclear giant cells (Dorothy Reed cells) (Fig. 5). Not a single case in this series was of follicular lymphoma.

In addition to the frank areas of lymphoma, 2 cases showed granulomatous areas associated with presence of lymphoid follicles and fibrosis.

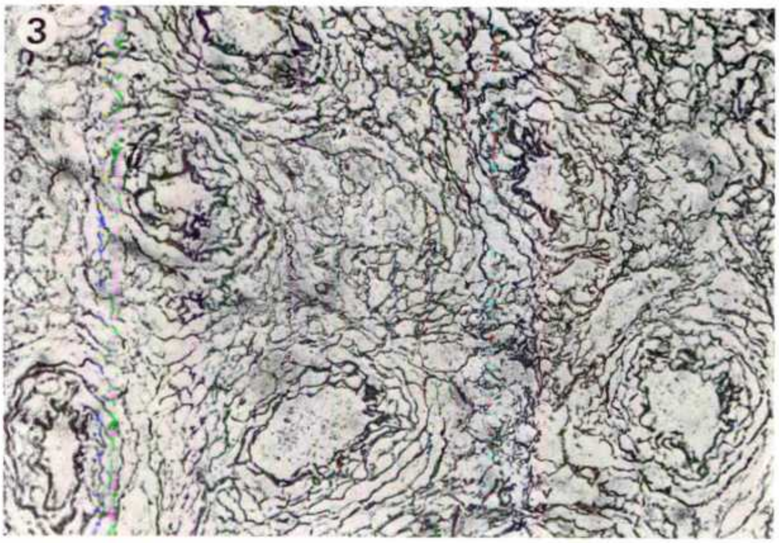

Fig. 3. Photomicrograph of the same area as Figure 2, after silver impregnation for reticulin showing network of concentric peritubular fibrils. Gomori's silver impregnation stain. × 90. (Path. no. 8392-E.)

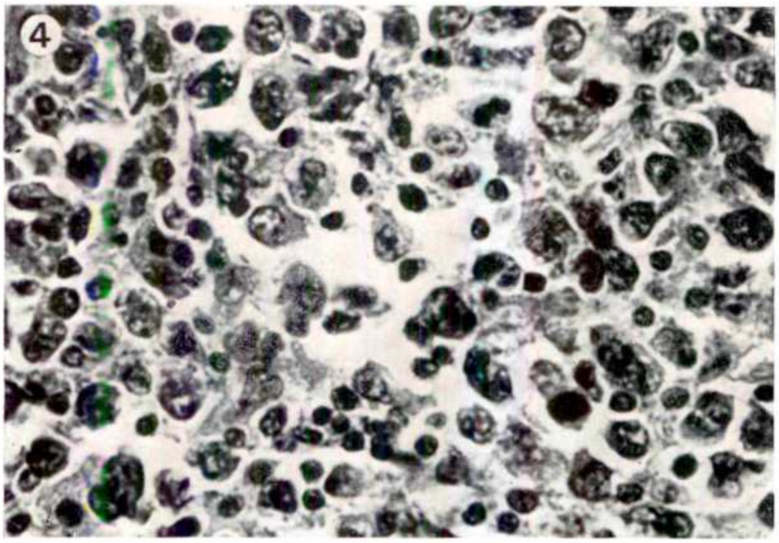

Fig. 4. Photomicrograph showing malignant lymphoma of testis of reticulum cell type. H & E. × 280. (Path. no. 3810-U.)

Irregular areas of necrosis were present. In 2 of 17 cases a few small granulomatous lesions consisting of macrophage cells and foreign body giant cells were seen. Calcified filarial parasites were identified in 2 cases; this was an incidental finding. The tunica vaginalis was thickened and infiltrated by lymphoma cells, in 3 cases. Sections from the epididymis showed involvement by tumour infiltration from the testis. Lymphoma cells were seen round the epididymis tubules widely separating them. The spermatic cord showed tumour infiltration in 3 cases only.

Discussion

Malignant lymphoma involving the testis is extremely rare and accounts for about 1% to 7% of all malignancies in testis (Dockerty and Priestley 1942; Collins and Pugh, 1964; Kiely *et al.*, 1970). In the records of Tata Memorial Hospital from year 1941 through 1972, lymphoma of the testis form 3·8% of 445 histologically proved cases of all testicular malignancies. Rosenberg *et al.* (1961) noted that testicular involvement was the initial manifestation in 6 of 799 males with lymphoma and that only 10 showed testicular involvement during the course of the disease. Similarly in our material consisting of 2,200 males with lymphoma, the testicular involvement was the initial manifestation in 15 cases, while 2 cases showed testicular involvement in the course of the disease.

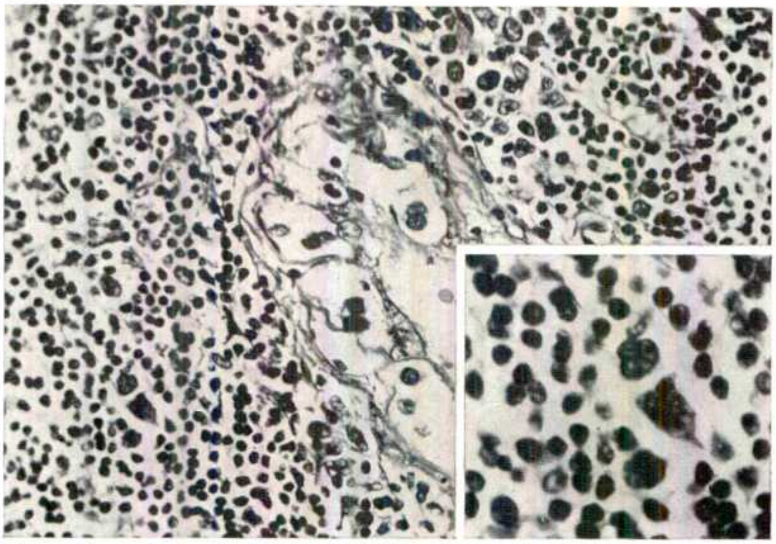

Fig. 5. Photomicrograph showing Hodgkin's disease of testis. Inset shows multinucleated giant cells of Dorothy-Reed type. H & E. ×280 and ×560. (Path. no. 9282-E.)

It has been observed previously that more than 50% of patients with bilateral testicular tumours have lymphomas (Hotchkiss and Laury, 1950; Eckert and Smith, 1963). We have seen this in our material also. Of 4 bilateral testicular tumours 3 were histologically proved to be malignant lymphoma and the 4th a seminoma.

Malignant lymphoma occurs more commonly in older men and is the most common type of testicular malignancy after 60 years of age (Kiely *et al.*, 1970). In the present series approximately 47% of patients were 50 years or more of age. In contrast to this only 5·6% of patients with other testicular malignancies in our material belonged to this age group. A few cases have been reported in children. In this study we have 2 cases of lymphoma occurring at the age of 5 years and 16 years respectively. Waddell in 1961 reviewing the literature found 7 cases of testicular lymphomas in children and reported 1 of his own.

Gowing (1964) in a study of 63 malignant lymphomas of the testis found 62 tumours composed of poorly differentiated cells of the lymphocytic series or of larger reticulum cells and designated all tumours belonging to this group as "Malignant lymphoma, poorly differentiated". Not a single case of Hodgkin's disease or follicular lymphoma was present. Givler (1969) in his autopsy study of 362 cases with lymphoma or leukaemia did not find microscopic testicular infiltration in 44 males with Hodgkin's disease. In our material of 17 cases there were 2 cases of Hodgkin's disease although none of the testicular tumours had characteristics of follicular lymphoma. Hamlin, Kagan and Friedman (1972) have reported Hodgkin's disease in 2 of their 9 cases of lymphoma of the testis.

Kiely *et al.* (1970) noted the frequent involvement of the skin and upper respiratory tract in patients with testicular lymphoma. Until now 5 cases with involvement of maxillary antrum have been described in the literature (Varney, 1955; Eckert and Smith, 1963; Hamlin, Kagan and Friedman, 1972). To this we would like to add 3 cases reported in this series of 17 cases. Cutaneous nodules confirmed by histology were present in 3 of our cases. The association of skin nodules with testicular tumour has been shown to be suggestive of a lymphoid tumour by Hotchkiss and Laury (1950).

Lymphoma presenting as a testicular swelling could be primary or secondary. The problem is whether the tumour is primary or whether it is the forerunner of a disseminated lymphoma. Our experience is different from that of Kiely *et al.* (1970) who designate a testicular lymphoma "primary" when no other clinical evidence of lymphoma is present at orchidectomy, but we have found that dissemination occurred within months during course of the disease in 9 patients in our series, in whom testicular tumour was the only manifestation at orchidectomy. Follow-up was available in 7 patients: all of them died within 6 months to a year after orchidectomy. A similar finding has also been observed by Hamlin *et al.* (1972). It is only in retrospect, as stated by Gowing (1964), after a patient has been without evidence of recurrence for some years, that malignant lymphoma of the testis may be accepted as a primary.

As far as the origin of any extranodal lymphoma is concerned it is not yet concluded whether the disease is unicentric or multicentric. Primary testicular lymphomas with survival of several years after orchidectomy favour unicentric testicular lymphoma. Two of our cases support Ficari's (1950) suggestion that lymphoma may develop in non-lymphoid organs following an inflammatory condition of several years duration. One of the two patients had mumps about 10 years previously and had testicular swelling of 6 years' duration which had increased in size during the past 2 years only. The other case gave history of filariasis 10 years before with swelling of left spermatic cord. Testicular swelling was of only 3 months' duration. The associated histologic changes of chronic inflammation seen in both these cases can be taken as an evidence in favour of this suggestion.

Rapid dissemination of the disease with death in a year or two after orchidectomy and infiltrative histologic picture rather than a destructive pattern are put forward in favour of a multicentric origin. Stout (1951) has observed that there are lymphosarcomas with 2 different disease patterns in respect to biological behaviour: the one which causes death in a short period with multiple involvement and the other with solitary involvement and long survival.

Testicular lymphoma is a highly malignant disease with poor prognosis. Nine patients in this series of 17 cases, died within 6 months to 1 year after orchidectomy. Two patients were alive 6 months and 5½ years after surgery with no evidence of disease, while 6 patients are lost to follow-up. Gowing (1964) has reported that 69% of the patients were dead within 2 years of surgery. A few long survivals are reported when lymphoma remained localised to the testis (Cohen *et al.*, 1955, Eckert and Smith 1963, Gowing 1964, and Kiely *et al.*, 1970). Unfortunately it is not possible to know whether lymphoma involving testis primarily is going to remain localised or disseminate.

Summary

The pathological and clinical features of 17 cases of malignant lymphoma of testis seen at Tata Memorial Hospital, Bombay, from the year 1941 through 1972 are presented. Malignant lymphoma accounts for 3·8% of 445 histologically proved cases of testicular malignancies in our material.

The material has been divided into 3 groups: (i) Testicular tumour as the only manifestation throughout the course of the disease (3 cases); (ii) Testicular tumour followed by dissemination during the course of the disease (12 cases); (iii) Testicular tumour following generalised lymphoma (2 cases).

Bilateral testicular tumours are rare but when they do occur malignant lymphoma accounts for the larger number of cases. Of 4 bilateral testicular tumours found in the total number of 445 testicular malignancies 3 belonged to malignant lymphoma group.

The maximum number of patients (14) were between the ages of 40 and 68 years. Two cases of lymphoma occurred in patients aged 5 years and 16 years respectively.

Malignant lymphoma of testis is a disease with a poor prognosis. The majority of the patients died within a year following orchidectomy. One patient is alive and free from disease for 5 years and 6 months after orchidectomy.

Hodgkin's disease of the testis is very rarely reported. We have seen 2 cases in our material.

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Rare Combination of Duplication of Genito-urinary Tract, Hindgut, Vertebral Column and Other Associated Anomalies

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Duplication of various portions of the genito-urinary tract, hindgut or vertebral column even individually are rare abnormalities. All of them occurring together in the same case is extremely rare indeed. The first case of diphallia was reported by Wecker (1609). We are reporting 2 cases, a boy and a girl with more or less identical anomalies involving genito-urinary tract, hindgut and vertebral column with slight differences depending upon their sex.

Case 1. R., male, newborn was admitted soon after birth as a case of anorectal atresia and double penis on 4th November, 1970.

He was a normally delivered third child of the family with a birth weight of 2,600 g. He had not passed meconium since birth but passed urine from both the penes at different intervals (Fig. 1). After examination and X-ray, a right transverse colostomy was done to relieve the acute intestinal obstruction and further detailed investigations done later.

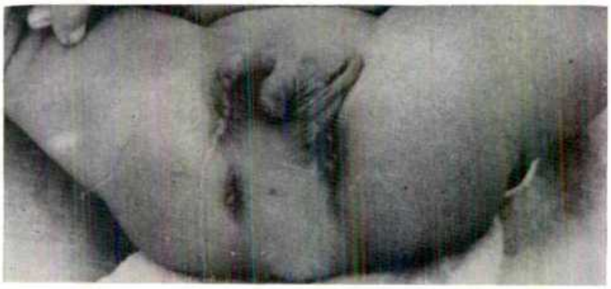

Fig. 1. R.—True complete diphallia with weak urinary stream from right side, bifid scrotum and 2 anal dimples, 2½ cm apart.

Detailed clinical examination, radiological investigations including plain X-ray abdomen, X-ray of the vertebral column, excretory pyelography, cysto-urethrogram, barium enema (done through the distal loop of the colostomy) and laparotomy revealed the following abnormalities:

(1) Kidneys—Left kidney normal in position and function. Right-sided pelvic kidney, hydronephrotic and poor function.

(2) Bladder, urethra and penis—Double bladder, double urethra, double penis, 1 penis in the midline, the second anteriorly and slightly to the right.

The left bladder drained into the midline penis with good stream and right bladder into the right anterior penis having a feeble stream of urine (Fig. 1).

Both the right and left kidneys drained into their respective urinary bladders, and these in turn emptied into their same side urethrae (Fig. 2). There was pneumaturia from the left urethra suggesting the presence of recto-urethral fistula.

Cysto-urethrogram showed free reflux from the right bladder into the right pelvic kidney (Fig. 2) which was hydronephrotic and poorly functioning. There was no reflux on the left side.

(3) Scrotum—Completely bifid with a normal testis in each half. There was a thin dark green line (raphe) with thick skin extending from left scrotum to the left anal dimple (Fig. 1).

(4) Anal region—There was no anal opening (anorectal atresia), but there were 2 anal dimples 2·5 cm apart separated by soft tissue and covered with pigmented skin. Barium enema done through the distal loop of the colostomy (after left perineal anoplasty) and subsequent laparotomy demonstrated duplication of hindgut from the

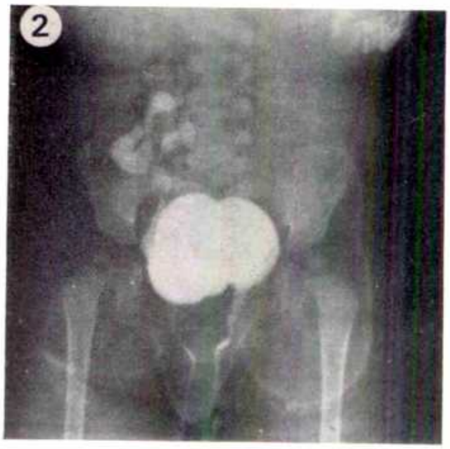

Fig. 2. Cysto-urethrogram, both sides, 2 separate bladders draining into their own urethrae with vesico-ureteric reflux on right side showing dilated pelvic kidney.

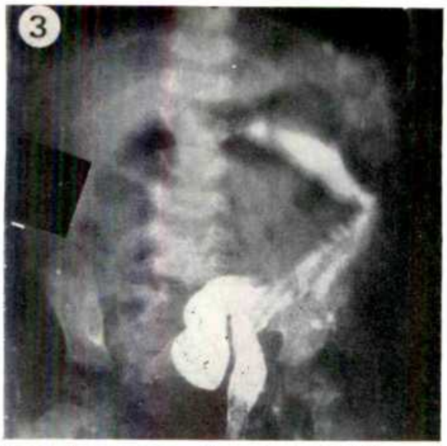

Fig. 3. Barium enema through the distal loop of colostomy, duplication of hindgut with right blind pouch.

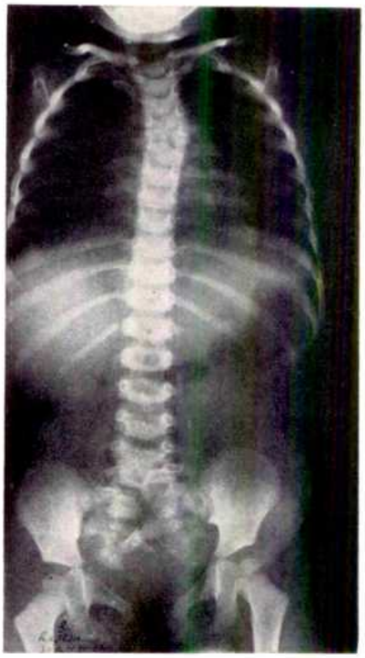

Fig. 4. Hemivertebrae—D5 left, first lumbar rib right side, duplication of sacrum with transverse disposition of coccyx.

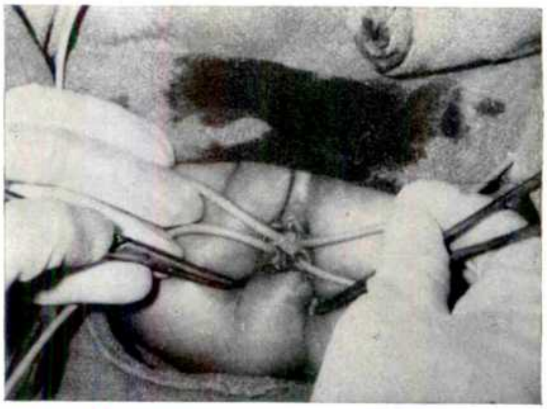

Fig. 5. A. B.—Perineum showing catheters into 2 urethrae, 2 vaginae and forceps pointing into right anal dimples and left anus.

middle of the transverse colon to the anal region with the right side as a blind pouch and the left opened into the perineal opening (Fig. 3).

(5) Vertebral column and pelvis showed the following anomalies (Fig. 4): (*a*) Hemivertebra D5 left side. (*b*) First lumbar rib on the right side. (*c*) Duplication of the sacrum with transverse disposition of the coccyx.

Case 2. A. B., 5-month-old girl brought to us in November 1972 with the history that at birth the doctor had told the mother that there was some developmental deformity of the perineum for which she should consult the surgeons later.

The child is the first in the family, born normally after a normal period of gestation with a birth weight of 2,860 g. The child passed urine and meconium normally after birth as expected and has grown normally up to this age. Reflexes were normal for her age.

Detailed clinical examination, radiological investigations, including plain X-ray abdomen, X-ray of the vertebral column, excretory pyelography, cysto-urethrogram and barium meal follow through revealed the following abnormalities:

(1) External genitalia—Asymmetrical labio-inguinal folds and labia majora. Well developed and elongated labia minora covering 2 urethral and vaginal orifices placed side by side. Two separate cervices seen through the 2 vaginal orifices (Fig. 5).

(2) Anal region—Two anal dimples somewhat anteriorly placed, separated by 2 cm of soft tissue. The left was open and functioning, the right one being imperforate (Fig. 5).

Barium meal follow-through showed caecum and ascending colon on the left side (Fig. 6).

(3) Meningocele—Bluish discoloration of the skin on the lumbo-sacral region covering the sacral meningocele (Fig. 7).

(4) Spine and pelvis—Plain X-ray showed maldevelopment of sacrum with spina bifida and meningocele and diastasis of pubic bones.

(5) Kidney—Excretory pyelography showed right kidney normal in position and function. The other kidney was situated at the level of L5 and S1 vertebrae on their right side, and showed a picture of crossed ectopia without fusion (Fig. 8). Each ureter drained into its respective urinary bladder, there being 2 separate urinary bladders, right and left (Fig. 9).

(6) Bladder and urethrae—Cysto-urethrogram confirmed the presence of 2 completely separate urinary bladders drained by 2 separate urethrae. Both the urethrae had a good urinary stream (Fig. 9).

Management and Results

The boy (R.) had several operations done in 4 stages; after the initial transverse colostomy to relieve the obstruction he had right nephrectomy, right cystectomy, amputation of the right anteriorly disposed penis, reconstruction of the scrotum, perineal reconstruction of left anus, side-to-side anastomosis of left and right rectum (lower blind pouch), disconnection of the recto-urethral fistula and closure of colostomy. The 2½-year-old boy is now as normal a child as he could have been.

No treatment was given to the girl (A. B.) as she had no symptoms and the deformities did not need any correction at this young age. We have kept her under observation and plan to watch her till puberty when she will need correction of the vagina

Discussion

Of all the rare duplication anomalies of lower urinary tract, duplication of the penis is the most common. According to the United States Census Bureau, it occurs once in 5·5 million births. The

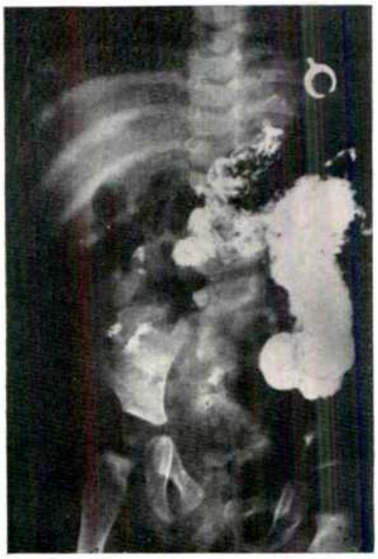

Fig. 6. Barium meal, caecum and ascending colon on left side.

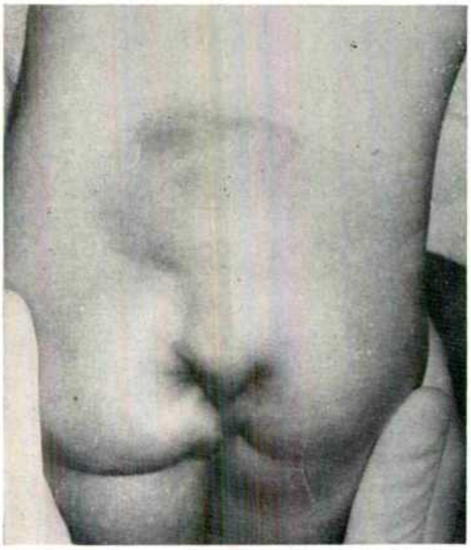

Fig. 7. Lumbo-sacral meningocele with bluish discoloration of covering skin.

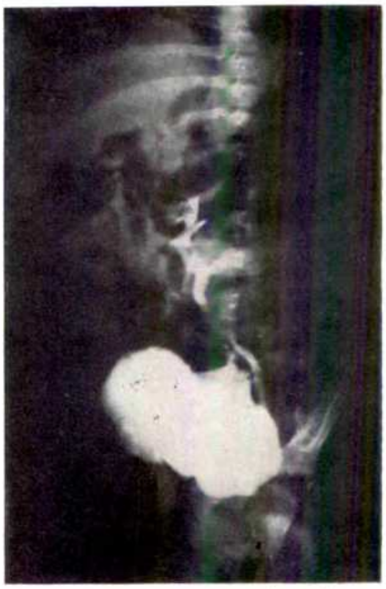

Fig. 8. Crossed renal ectopia without fusion on right side.

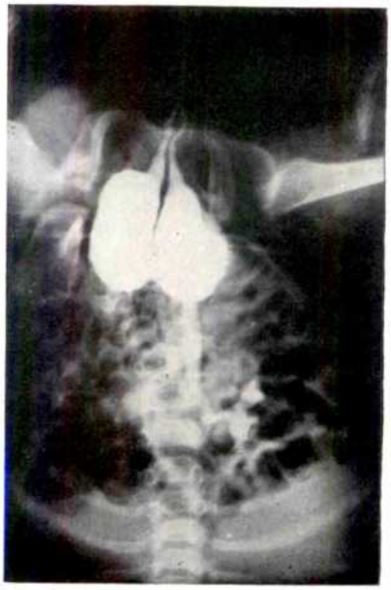

Fig. 9. Intravenous pyelograph crossed renal ectopia right side, 2 completely separate bladders with urethrae.

first case of diphallia was reported by Wecker (1609). 70 total cases from literature (excluding the United States) but including their own 2 were reported by Campbell (1937) and a few more have been added since then. Savir, Lurie and Lazebnik (1970) while reporting their 1 case of diphallia quoted that over 100 cases of double urethra have been reported by Braband and Anand (1965).

46 cases of double bladder have been reported in the literature by Campbell (1970). Abrahamson (1961) reported only 16 cases of complete duplication of bladder, urethra, and penis with each kidney emptying into its own bladder which in turn emptied through its own urethra and penis. Janknegt, Daenekindt and Moonen (1968) stated that only 18 cases of double bladder and urethra have been reported.

Rodriguez (1965) reported a 5-day-old baby with double penis and urethra. The right side had epispadias and the left hypospadias. One of our own children has bifid microphallia with bilateral glandular epispadias with other anomalies which have not yet been reported. Campbell (1970) reported a case of Allsner where the penis terminated in 2 glans. One was used for voiding urine and the other for seminal ejaculation.

Satter and Mossman (1958) described a case of double bladder and double urethra in a female child. Swenson and Oeconomopoulos (1961) reported a girl who had duplication of the entire lower genito-urinary system, each ureter opening into its respective bladder.

Volpi (1903) described a case which had double penis, urethra and bladder with bifid scrotum, horseshoe kidney with a single ureter opening into the left bladder and imperforate anus. Duplication of urogenital and lower intestinal tract has been reported by Fischer (1952).

Pelvic kidney is found in 1 : 800 cases, more common in males and 3 times more common on the left side than the right. Our child (R.) had a pelvic kidney on the right side with clinical bacteriological and radiological evidence of urinary infection. Henley and Rankin (1971) reported 21 cases of pelvic kidney out of which 48 % had urological symptoms. The findings of Ward (1965) are also the same. 18 out of his 38 cases had symptoms (47 %).

Crossed renal ectopia is still more rare. Abeshouse and Bhisitkul (1959) reported from the literature, 337 cases of crossed renal ectopia with or without fusion. The fusion may be end-to-end, side-to-side, S- or L-shaped.

Only a few cases are reported in the literature who have duplication of the genito-urinary tract and hindgut as well as the vertebral column. The vertebral defects are either spina bifida or hemivertebra. We have not come across any case with duplication of the sacrum in English literature. Duplication of the sacrum as it is, is an extremely rare anomaly and even the most experienced of orthopaedic surgeons have not seen more than 1 or 2 cases in their career (Sankaran, 1973).

Various people have tried to classify double urethra and/or double bladder into various groups.

Taruffi 80 years ago divided double urethra into 4 types (Campbell, 1970):

Type 1. Blind ending canals, in which the canal opens on the surface of the penis but does not communicate with the urethra or the bladder, or the canal opens into the urethra but does not open on the surface of the penis.

Type 2. An accessory canal which conveys seminal fluid and is independent of the urethra. This has been referred to as seminiferous canal.

Type 3. An accessory canal which communicates with both the urethrae and the surface of the penis. This may be termed simply a bifurcation of the urethra or an uriniferous canal.

Type 4. Certain congenital urethral fistulae which usually arise from defects in the embryonic cloaca.

Senger and Santare (1951) classified congenital duplication of bladder into the following 3 major groups:

(1) Sagittal or longitudinal.
(2) Frontal or transverse.
(3) Multilocular bladder.

Abrahamson (1961) classified double bladder into 6 groups:

(1) Sagittal division:
  (*a*) Complete reduplication of the bladder.
  (*b*) Incomplete reduplication of the bladder.
  (*c*) Complete sagittal septum.
  (*d*) Incomplete sagtital septum.
(2) Frontal division—incomplete frontal septum.
(3) Multispastate bladder.
(4) Hour glass bladder.
(5) Trigonal curtain.
(6) Bladder neck valve.

The incidence of this anomaly is so rare that no one person could have sufficient cases of his own to give a proper classification. In any case, these classifications can apply only when the anomaly is single, but in our 2 cases there are so many anomalies in each that they could not be fitted into any of the above groups.

Embryology

The boy appears to be a case of caudal duplication. The hindgut along with cloaca is duplicated hence the double distal third of transverse colon, double descending colon, double bladder and double rectum. The perineum also shows duplication resulting in 2 anal dimpling and diphallus. The later anomaly is usually described as a mesodermal defect due to over-development of cloacal membrane and can occur quite independent of the hindgut duplication.

Female Child

Duplication of urogenital sinus, urinary bladder develops from the urogenital sinus and vagina by canalisation of the sinovaginal bulbs arising from endoderm at the common opening of Mullerian ducts in the pelvic portion of urogenital sinus. If the sinovaginal bulbs fail to fuse or do not develop at all, this will result in double vagina.

Summary

Two children, one male and one female have been presented with more or less identical rare congenital deformities of genito-urinary tract, hindgut and vertebral column.

Both the children had completely separate urinary systems, each comprising 1 kidney ureter, bladder, urethra and penis in the boy with no communication at any level.

The genital organs in both cases were completely duplicated, the boy having 2 penes and double scrotum containing a normal testis in each and the girl had 2 vaginal orifices and 2 uteri as demonstrated by 2 cervices projecting into the 2 vaginae (no other test to demonstrate the 2 uteri were done).

Both the children had duplication of hindgut and anorectal atresia, complete in the boy and partial in the girl. The girl also had reverse rotation of the hindgut.

Both the children had defects in the vertebral column. The boy had hemivertebra, first lumbar rib on the right side and double sacrum. The girl had malformation of the sacrum with spina bifida and diastasis of pubic bones.

The anomalies in the girl on the whole showed an attempt at reduplication of single organs and fusion of paired ones.

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British Journal of Urology (1974), **46**, 583

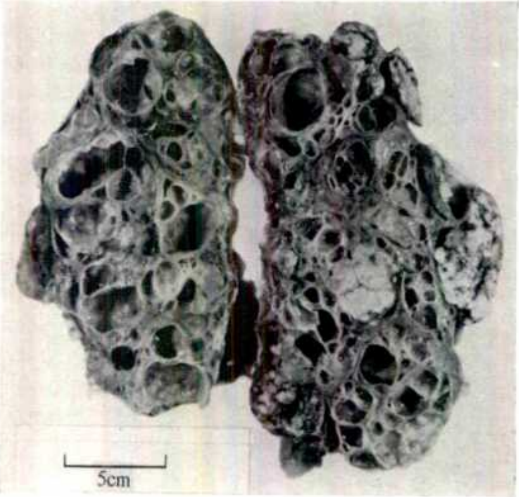
·Short Case Reports

Cerebral Aneurysm, Renal Cysts and Hamartomas in a Case of Tuberous Sclerosis

A 24-year-old man died after a subarachnoid haemorrhage. Necropsy revealed a ruptured saccular aneurysm of the right middle cerebral artery, gross hypertrophy of the left ventricle and tuberous sclerosis of the brain. Both kidneys were enlarged, and their parenchyma replaced by cysts (see Figure); histology confirmed a diagnosis of polycystic disease. There were solid, partly necrotic nodules (up to 5 cm diameter) in the left kidney, and a few smaller nodules in the right kidney; microscopy showed these were angiomyolipomas. There was also soft tumour in the para-aortic nodes; this consisted of papillary formations and trabeculae of spindle cells, and was considered to be hamartomatous rather than metastasis from a renal neoplasm.

Renal hamartomas are found in the majority of cases of tuberous sclerosis. Extrarenal involvement by tumour limited to para-aortic lymph nodes has previously been reported by Feriz (1930). Renal cysts have been noted in patients with tuberous sclerosis; 4 reports described young adults with polycystic kidney disease and tuberous sclerosis. Others have reported this association in infants, and Potter (1972) describes 3 such infants as having adult-type polycystic kidneys (Type III). Cerebral aneurysm has not been reported in other cases of tuberous sclerosis.

I wish to thank Mr J. Brice and Dr A. Dayan for their help in preparing and permission to publish this report.



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A Solitary Metastasis to the Bladder from a Renal Adenocarcinoma

A right-sided renal adenocarcinoma (Fig. 1) was removed from a 56-year-old man with a 4-week history of haematuria. Cystoscopy at the time of nephrectomy was normal. Gross renal vein involvement was present at the time of nephrectomy, but clearance appeared complete. Initial progress was satisfactory, but further haematuria occurred after 8 months. Cystoscopy demonstrated an encrusted lesion in the dome of the bladder, but because of the extent of the original lesion, the prognosis was thought to be poor, and no further investigations were carried out. The patient remained well, but was eventually re-admitted 3 years after nephrectomy because of increasing haematuria. Cystoscopy showed an increase in size of the lesion previously noted, and biopsy demonstrated the same appearances as the original renal lesion. Since no other metastases were evident, partial cystectomy was performed; histology (Fig. 2) confirmed the metastatic nature of the lesion, which was confined to the bladder mucosa. Subsequent progress has been satisfactory.

Sixteen reported cases of metastases to the bladder from renal adenocarcinoma were reviewed by Alarcon and Melick (1968), who added 1 further case of their own. Either a haematogenous or a urinary route of spread is possible; opinion in the literature has been equally divided between the two (Macalpine, 1948). In 7 of the reported cases the bladder metastasis appears to have been solitary, as in this case, but no case of long-term survival after resection has been recorded. Nevertheless prolonged survival after resection of solitary metastases elsewhere from renal adenocarcinoma is well described, and partial cystectomy therefore seems to be well justified.

I am grateful to Mr Patrick Smith for his permission to publish this case, and to Dr R. L. Bishton for his help with the pathology.

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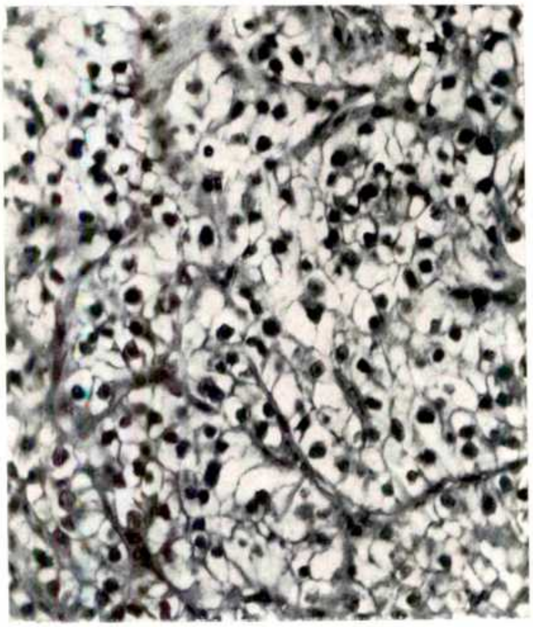


Fig. 1.

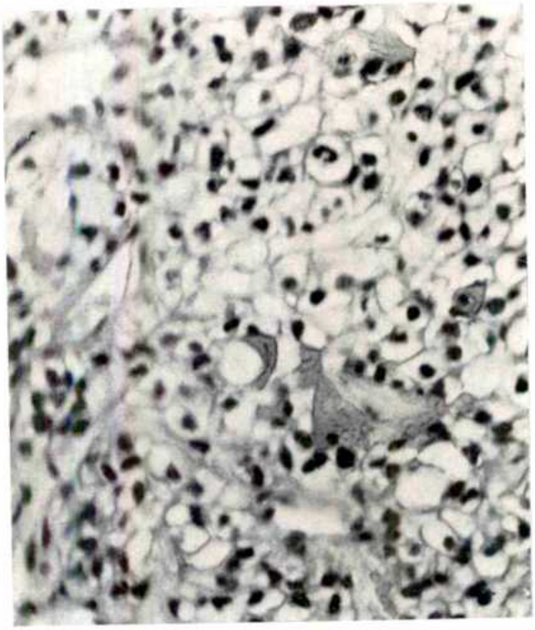


Fig. 2.

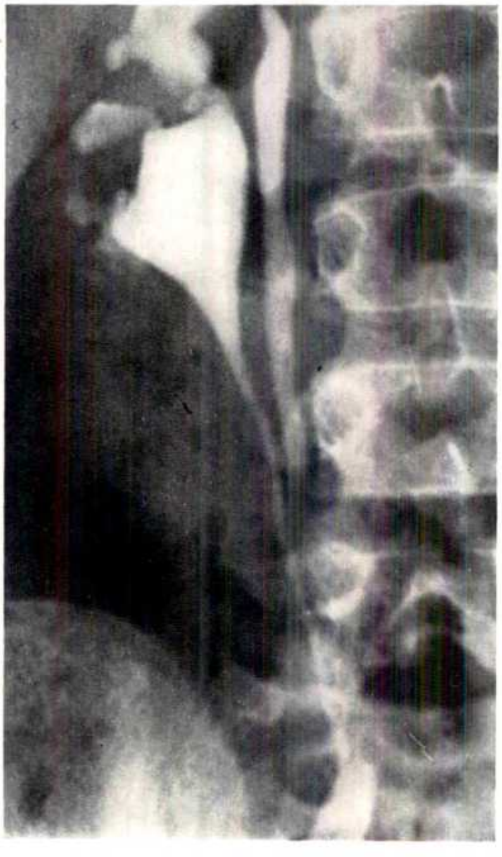
British Journal of Urology (1974), **46**, 585

Unilateral Triplication of the Ureter

A 6-year-old schoolgirl was referred to the Royal Berkshire Hospital, Reading, in October 1968, having had intermittent episodes of generalised abdominal pain, irritability and fever over the previous 5 months. She had been continent from the age of 18 months and had never had any urinary symptoms. Urinalysis on 3 occasions, however, had shown an infection, which responded each time to a course of the appropriate antibiotic. An intravenous pyelogram showed a small contracted right kidney with clubbing of the calyces and relatively poor excretion. The left kidney and ureter were normal. Treatment by long-term nitrofurantoin kept the child symptom free for the next 2½ years, except on 3 occasions when the treatment was temporarily ceased and the infection recurred each time. In March 1971 a micturating cystogram (Fig. 1) showed free reflux up a dilated right ureter which was seen to divide at lumbosacral junction level. Cystoscopy showed 2 right ureteric orifices, situated alongside each other on the inter-ureteric bar, and the rest of the bladder was normal.

Because of the recurrent urinary infection and the pyelonephritic kidney, right nephro-ureterectomy was performed through a loin incision on the 7th May 1971. At operation (Fig. 2) 3 ureters were found arising from the 3 pelves of a small shrunken pyelonephritic right kidney. The ureters from the uppermost and lowermost pelves fused at the pelvic brim, while the third ureter from the middle pelvis continued independently down to the bladder. The patient made an uninterrupted recovery, being discharged home on the 10th postoperative day, since when the urine has been sterile and the patient symptom free.

Fig. 1.



Unilateral triplication of the ureter is one of the rarest anomalies of the urinary tract. In reviewing all 44 previously reported cases, 3 distinct types emerged. This case is an example of the least common type—double ureter with 1 bifid—in which 3 ureters leave the kidney but 2 fuse, resulting in 2 intravesical orifices. In complete triplication the 3 ureters remain independent and terminate intravesically, or occasionally one of the ureters has an ectopic orifice. Trifid triplication is the commonest type, when all 3 ureters fuse resulting in only 1 intravesical ureteric orifice.

I would like to thank Dr Joyce Burke and Mr Conrad Latto for allowing me to present this case history.

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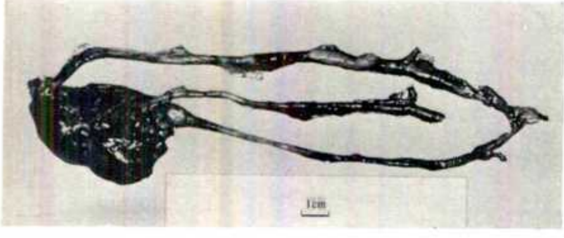
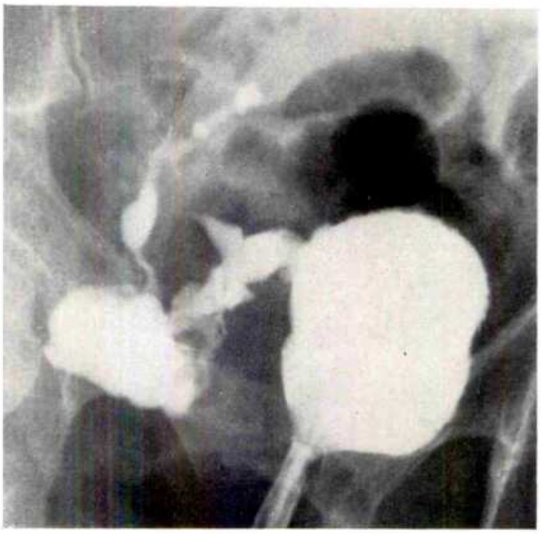
Fig. 2.



British Journal of Urology (1974), **46**, 586

Appendico-Vesical Fistula—A Rare Complication of Acute Appendicitis

A 62-year-old man was admitted as an emergency because of abdominal pain, fever, lassitude and anorexia of 2 weeks' duration. The right iliac fossa was very tender, with a palpable mass 5 × 5 cm in size which was non-mobile and of hard consistency. Emergency drip-infusion urography showed good secretion bilaterally, marked dilatation of the right kidney and ureter and deformation and displacement of the urinary bladder. 36 hours later faecaluria and pneumaturia appeared. Urgent cystography showed a fistula between the bladder and right colon with partial extravasation of the contrast medium into the perivesical area (see Figure). Laparotomy revealed a huge retroperitoneal abscess. The caecum was thick and inflamed; the tip of the appendix was visualised only after mobilisation and the rest of it communicated with the retroperitoneal abscess. The urinary bladder was adherent to the abscess and part of its dome had to be excised. A huge amount of pus was drained from the abscess and the necrotic tissue was excised. I.V.P. and cystography performed some time later showed no abnormalities and the patient was found to be in good health.



Appendico-vesical fistula, a very rare complication of acute appendicitis, occurs either as the result of direct penetration of an inflamed appendix into the urinary bladder or through a periappendicular abscess communicating and draining into the bladder, as in the above case. Kellogg (1938) was the first to report a series of cases with such a fistula and since then the number of reported cases has been brought up to more than 50 (Fitzpatrick, 1961). It is stressed that the appearance of pneumaturia and faecaluria should be considered an indication for urgent investigation and operation.

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British Journal of Urology (1974), **46,** 587

A Case of Vesico-Uterine Fistula

Mrs E. S. was first seen 20 days after a lower segment Caesarean section for a posterior face presentation. Two previous deliveries had been normal. Her main complaint was of urinary incontinence day and night. Clinical examination showed no abnormality. An intravenous pyelogram was normal. Cystoscopy showed no abnormality except that on the posterior wall there was a tiny hole. This was catheterised quite easily, but the catheter was not seen in the vagina as expected. Injection of water through the catheter came out profusely from the cervical os. A plain film showed the catheter coiled in the uterus and injection of contrast gave a uterogram (Fig. 1). A cystogram the following day showed a small tract leading to the uterus (Fig. 2). She was then discharged home. She was readmitted 5 months later. During this time she had continued to be wet, though passing small quantities of urine as well. She had menstruated on one occasion, but did not notice blood in her urine.

Operation. Lower paramedian incision. Extraperitoneal approach. The bladder was opened. The 2 ureters were catheterised and a probe was introduced into the fistula. The bladder was incised down to the fistula which was excised. The vaginal vault was opened inadvertently; the opening was subsequently used for the insertion of a tissue drain down the vagina. The bladder and uterus were closed in 2 layers with catgut. Extraperitoneal fat was inserted between the two viscera. Another drain was placed in the vesico-uterine pouch and the bladder was drained per urethram by a Foley catheter. Apart from the development of thrombosis of the left femoral vein, which was treated with anticoagulants, her recovery was very satisfactory. A postoperative cystogram showed no sign of a fistula.

Only 13 cases of vesico-uterine fistula have been described in the literature. The main cause is lower segment Caesarean section. The 2 striking symptoms in most of them are menouria (Youssel, 1957), *i.e.*, cyclical haematuria, and the absence of urinary incontinence (Sammour, 1970). Our patient did not notice bleeding per urethram during menstruation and she had urinary incontinence. The diagnosis is sometimes established on the operating table (Willson-Pepper, 1965) but in our cases the incontinence drew attention to the fistula thus making the diagnosis easy.

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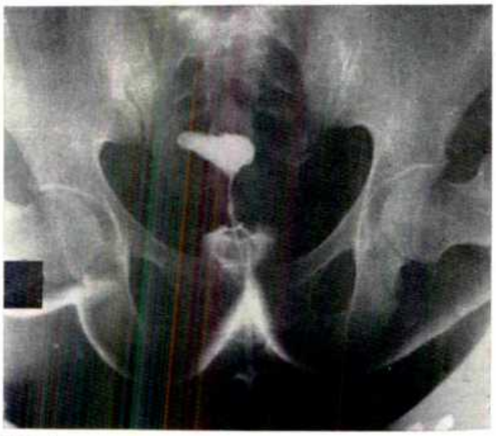

Fig. 1

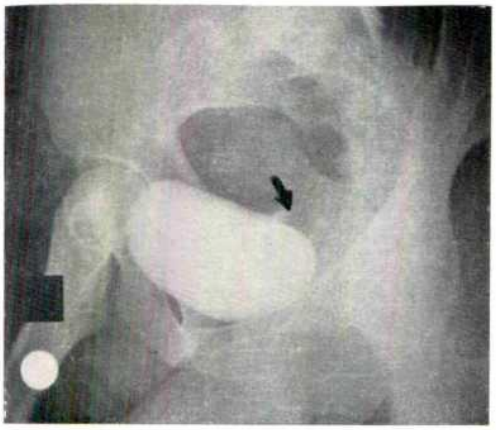

Fig. 2

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Book Reviews

Bladder Control and Enuresis. Edited by I. KOLVIN, R. C. MACKEITH and S. R. MEADOW (Clinics in Developmental Medicine Nos. 48-49). Pp. 328, with 5 illustrations and numerous tables. London, Heinemann Medical Books Ltd. 1973. Price £6·20.

The origin of this book lies in a colloquium on Recent Advances in the Knowledge of Bladder Control in Children, held under the auspices of the Department of Psychological Medicine at the Royal Victoria Infirmary, Newcastle upon Tyne. At this colloquium the subject of enuresis was tackled at considerable length from every aspect and by experts in every field. The Editors of the volume have not simply published the papers given, but have selected, modified, and, in some instances, supplemented the original material. It has thus been possible to produce a full and exhausting account of the subject, and the book will undoubtedly be the source from which our basic knowledge of the subject of enuresis is derived for very many years. We are given a full discussion of the normal physiological and psychological development, a concise summary of the physiology of micturition by the Editor of this *Journal*, and a discussion of the epidemiology of enuresis. Giggle micturition receives the attention which it deserves but so seldom receives in textbooks. Dr Jonge contributes a chapter on what he calls "the urge syndrome", in which little girls suddenly feel the need to compress the urethra, but curiously fails to discuss the rather evident psychosexual aspects of this act.

Enuresis lends itself to clinical investigations, and many of the contributors have undertaken such studies, so that the diverse problems of genetics, of depth of sleep, of E.E.G. findings and of the association with urinary infections are fully dealt with. Urodynamics does not receive quite as full a discussion as one would expect nowadays, though there is a report on cystometry and the importance of a small bladder capacity in the genesis of enuresis. Psychological factors are dealt with at length, but happily without overstating the case for cure by psychiatry.

This is undoubtedly a book which should be available for reference in medical libraries, though few of us will feel inclined to read it from cover to cover.

D. I. W.

Glomerulonephrititis. Morphology, Natural History and Treatment. In 2 parts. Proceedings of an International Symposium, Royal Melbourne Hospital. February 1972. Edited by PRISCILLA KINCAID-SMITH, T. H. MATHEW and E. LOVELL BECKER. Pp. 1238, with 521 illustrations. John Wiley & Sons, Ltd. 1973. Price £22·50.

These two volumes on glomerulonephritis edited by Dr Kincaid-Smith and her colleagues are the recorded proceedings of an international symposium held at the Royal Melbourne Hospital in February 1972, and as such they must represent the most up-to-date and comprehensive treatise on glomerulonephritis and related conditions yet published. Progress in the understanding of this most confusing yet fascinating group of diseases has advanced with bewildering rapidity in the last 10 years.

From some 21 centres 37 acknowledged world experts in the fields of clinical nephrology, immunology, histopathology, electron microscopy and haematology have individually and in groups been called upon to summarise their studies for presentation. Several contributions were received on almost every important topic.

One of the main objects was to agree on a common and internationally accepted nomenclature by which the various disease entities could be recognised, and a large measure of success has been achieved.

From these beautifully produced volumes with their numerous exquisite photomicrographs depicting renal histology, emerges the clear message that glomerulonephritis can no longer be categorised by vague clinical descriptions. Accurate diagnosis depends on morphological features whose complete delineation may require high quality light microscopy, immunofluorescence studies and electron microscopy. Employment of these and other immunological techniques in many centres has allowed a classification to be evolved, which, though still incomplete, relates to certain predictable patterns of natural history and response to treatment. The layout of the book makes it particularly useful as a reference work; and the discussions of the contributors revealing their doubts and misgivings are not only entertaining, but also make one's own confusion easier to bear.

P. R. U.

Mechanisms of Hypertension. Edited by M. P. SAMBHI. Pp. 390, well illustrated. Amsterdam: Excerpta Medica. 1973. Price not stated.

It is rare to find a medical text which is compulsive reading, but this book was difficult to put down. It is a well presented book and has appeared within a reasonable time following the conference which it reports. It consists of a series of papers presented by leaders in the field of hypertension and renal physiology at a conference in Los Angeles in March 1973. The papers are largely in the form of reviews including descriptions of the authors' own work and are followed by critical discussion involving workers who have made original contributions in the field. The book is well organised to give an orderly cover to most aspects, clinical and physiological, of hypertension and sodium balance.

Dr Grollman opens with an excellent review of work in experimental hypertension and may be excused for a sweeping dismissal of the adrenal cortex in the pathogenesis of essential hypertension; this controversy is well aired later in the book. A. C. Guyton brings us up to date with his thoughts on the central role of the kidney and sodium homeostasis in the control of blood pressure and, although his explanations are of necessity rather brief, they are convincing and interesting even to the clinician because his ideas give some rational basis for the choice of treatment in various types of hypertension. Dr Thurau again leads us through the controversy over the role of the macula densa in the control of renin and this provokes lively discussion. For the clinician there is a report from Dr Hunt of a comparison of medical and surgical treatment for renovascular hypertension and, although this was not a controlled trial with random allocation to medical or surgical treatment, it does provide support for the value of surgery and provoked useful discussion. Perspective on the role of the adrenal cortex in hypertension is given by Dr Genest's historical account of the work—some of it from his group—which led to our present state of knowledge. A small criticism of this account is the failure to mention the crucial contributions of Luetscher and of Tait in the early 1950s. Dr Luetscher reporting his recent work gave some interesting new observations and ideas on the differentiation of adrenal adenoma and hyperplasia in Conn's Syndrome. Kallikrein and prostaglandins (until recently mysterious substances to many of us) were put in place at least provisionally. The importance of relating renin and angiotensin to sodium status was clearly demonstrated by the Glasgow group.

The book cannot be too highly praised, giving as it does an up-to-date review of the field of hypertension written by acknowledged world leaders in the field. I would consider it a good investment for anyone engaged either in research into hypertension or in the clinical management of hypertensive patients.

R. W.

Conferences and Courses

UROLOGICAL SOCIETY OF AUSTRALASIA

The 28th Annual General Meeting of the Urological Society of Australasia will be held in Sydney from 13th to 17th April 1975.

Further information may be obtained from the local Secretary:

Mr J. H. ROGERS,
100 Carillon Avenue,
Newtown,
N.S.W. 2042,
Australia

SECOND ANNUAL PEDIATRIC NEPHROLOGY SEMINAR—DYNAMICS OF PROGRESSIVE NEPHROPATHIES, THEORETICAL AND PRACTICAL ASPECTS

JANUARY 2nd to 7th 1975

The above course—Dynamics of Progressive Nephropathies—Theoretical and Practical Aspects —will be held at the Americana Hotel, Bal Harbour, Florida.

Fee: Physicians in Practice – $175
Physicians in Training – $75
Nurses – $100

Further information may be obtained from:

JOSE STRAUSS, M.D.,
Division of Continuing Medical Education,
University of Miami School of Medicine,
P.O. Box 520875 Discayne Annex,
Miami, Fla. 33152

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The list of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal*, *i.e.* in anatomical order beginning with papers on the kidney.

- A general section is included at the end.

KIDNEY

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“Effective treatment for U.T.I without side~effects.”

Everyone knows that nitrofurantoin can cope with urinary tract infections.

Everyone knows that some patients can't cope with nitrofurantoin.

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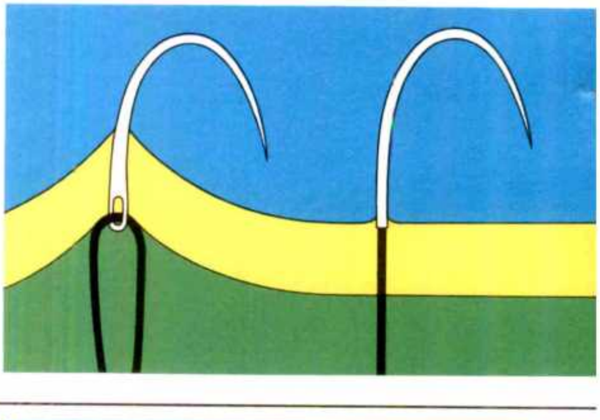

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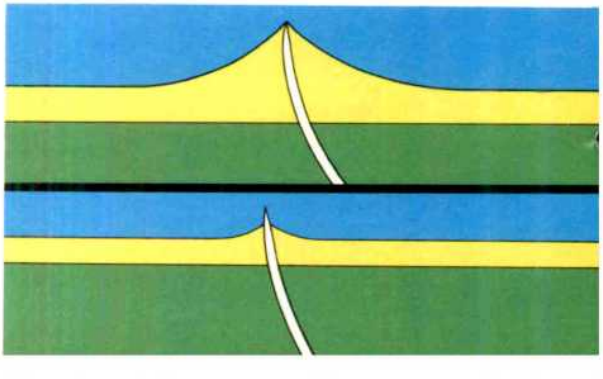

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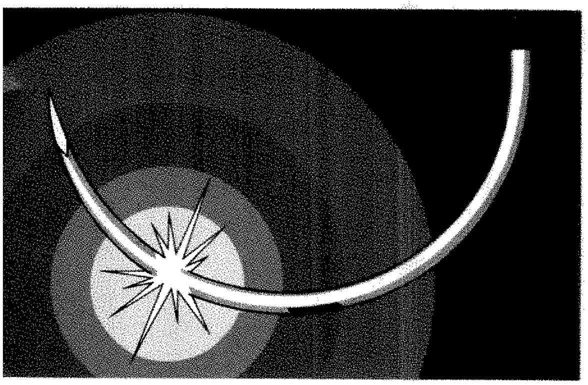

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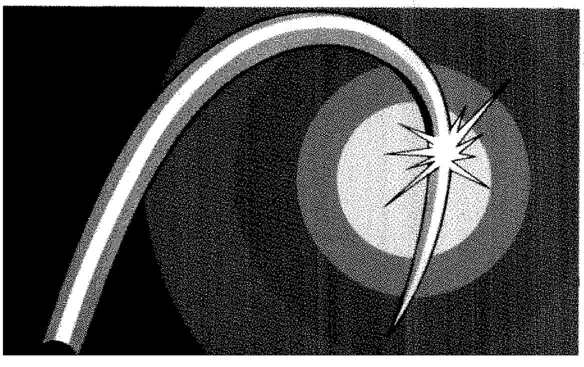

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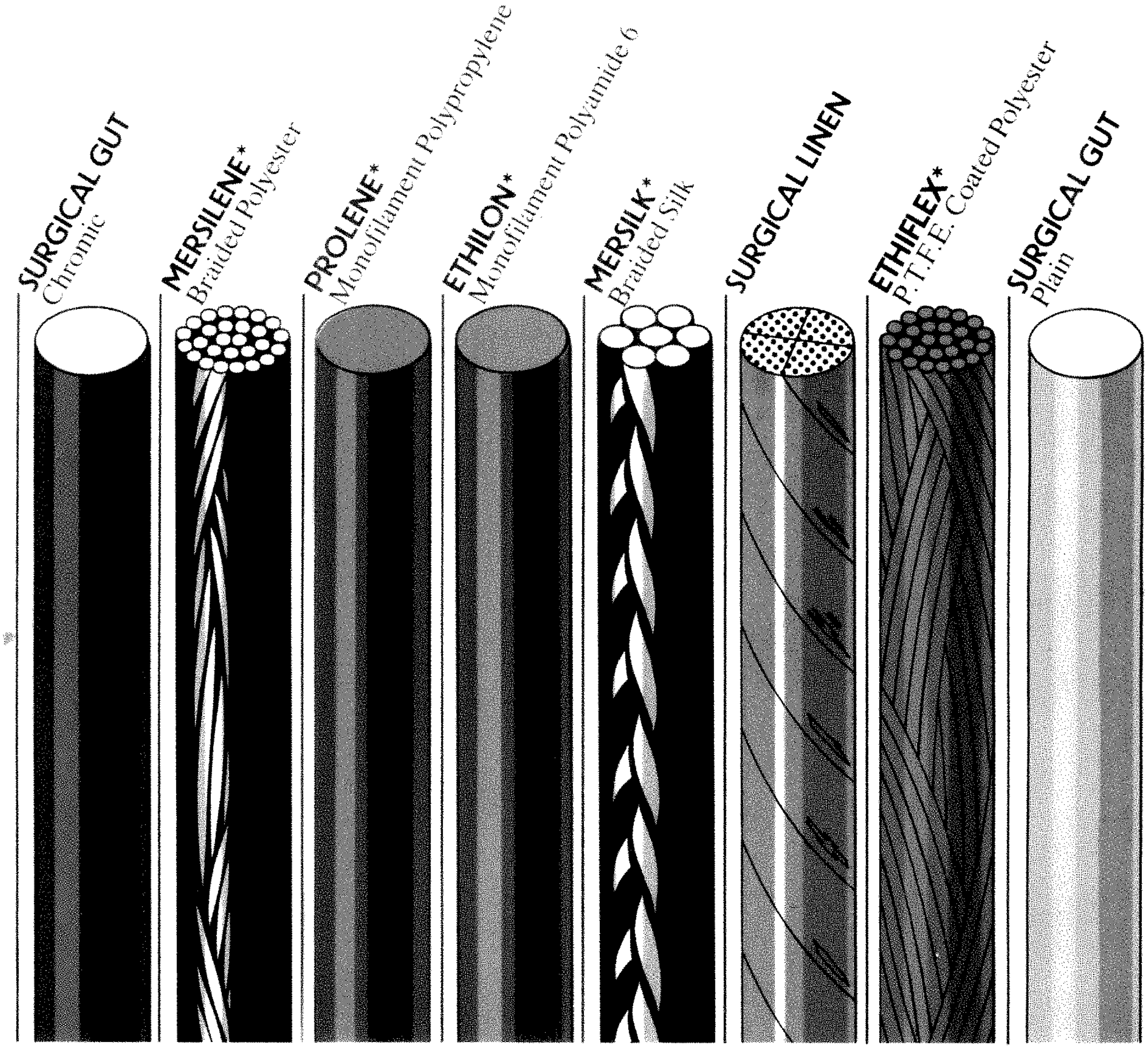

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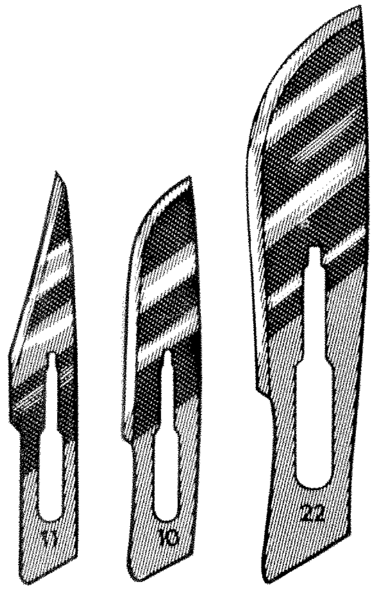

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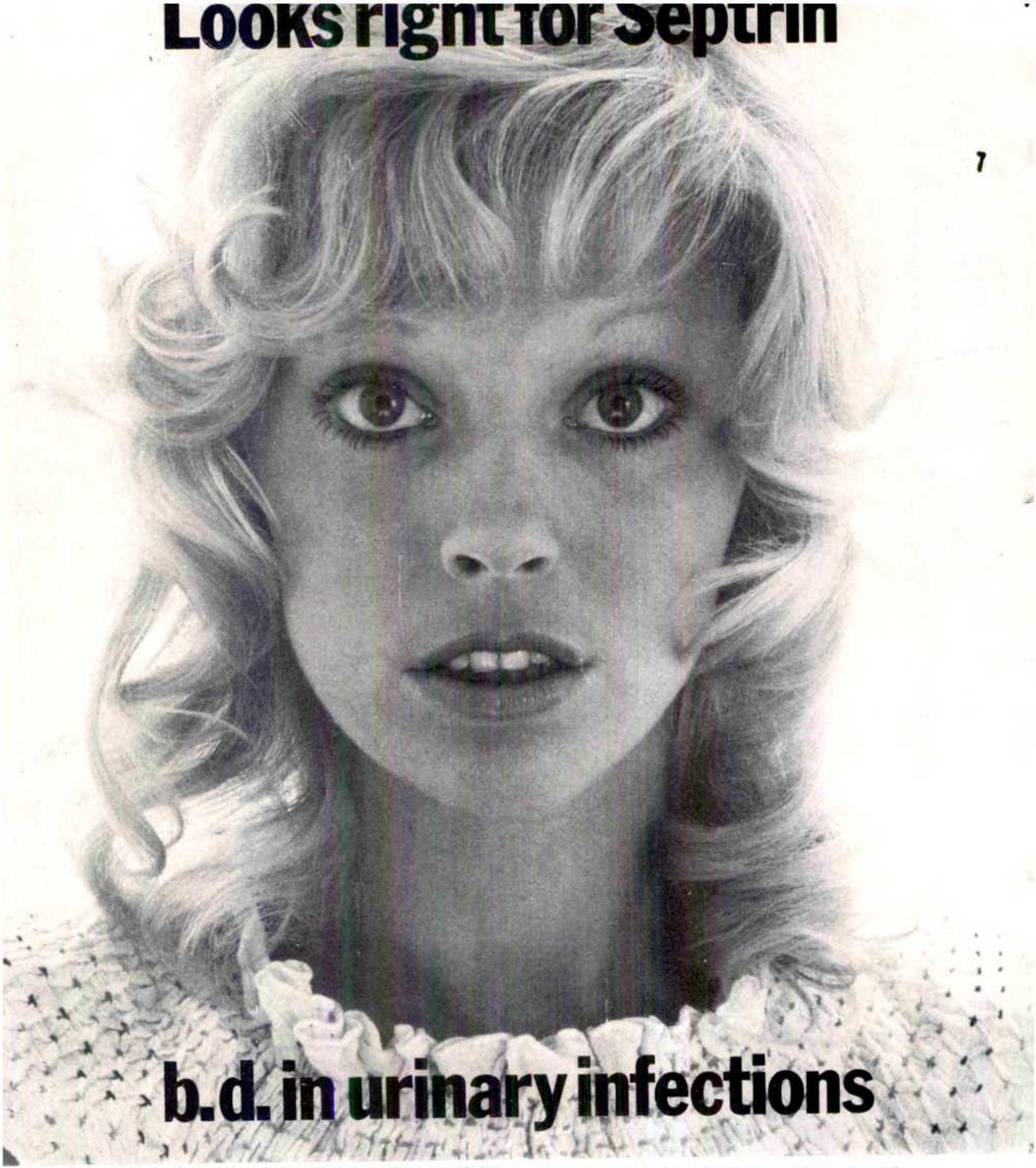

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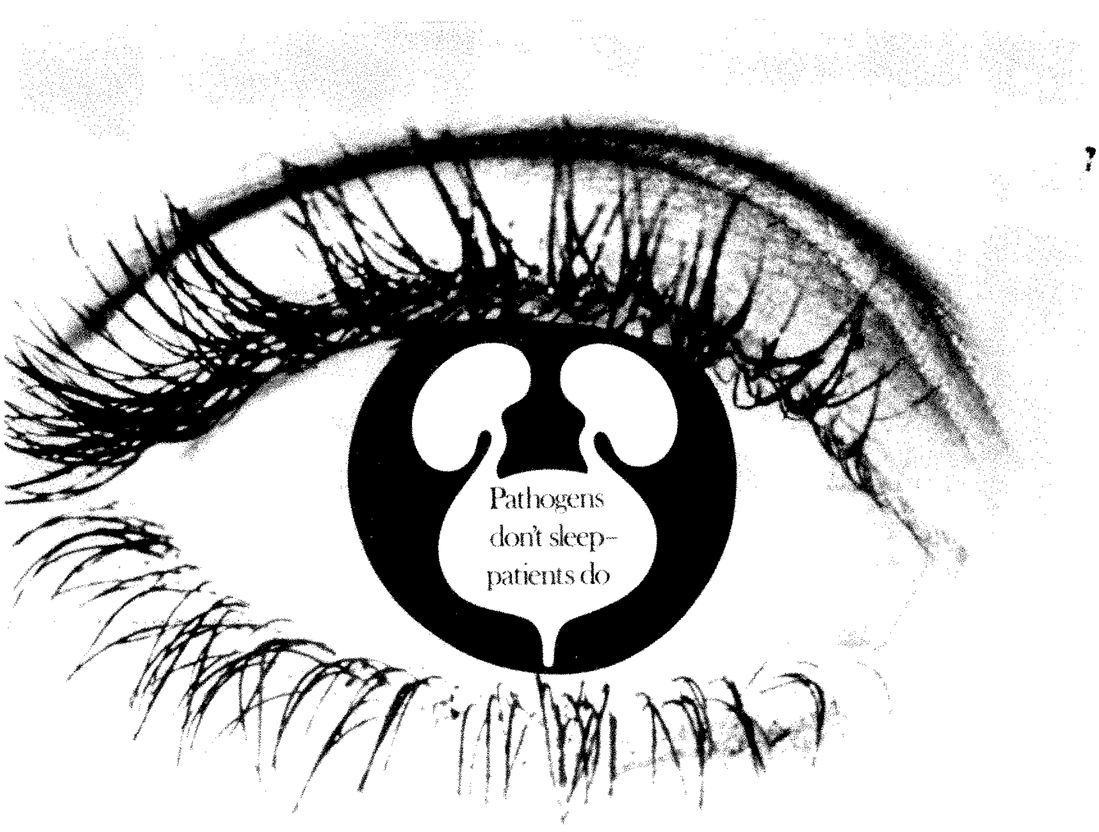

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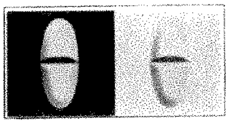

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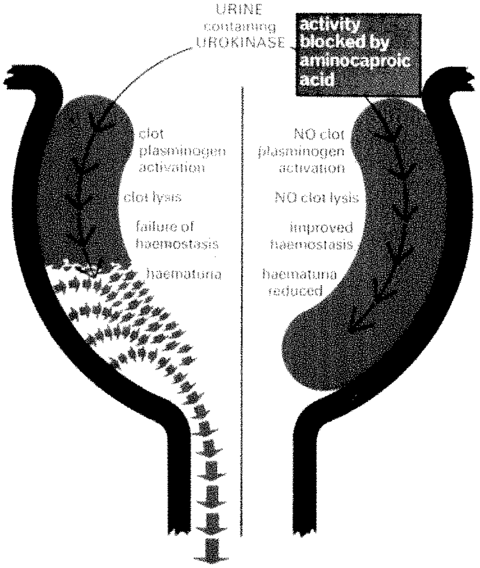

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LIVING OR DYING: Adaptation to Hemodialysis *edited by* **Norman B. Levy**, *State Univ. of New York, Brooklyn. Introduction by* **Belding H. Scribner.** *(13 Contributors)* Psychological aspects of hemodialysis is the subject of this book, the first of its kind to study this problem. Leading authorities on the major problems in psychological adaptation to this procedure discuss special psychiatric problems of the child receiving hemodialysis, the uncooperative hemodialysis patient, psychological factors determining survival and changes in sexual activity in hemodialysis and transplantation. Also presented are the proceedings of a panel held at the 1972 meeting of the American Psychiatric Association which was composed of notable contributors to the study of the psychological problems of these patients. Written primarily for psychiatrists, nephrologists and internists, this book should also be of interest to patients who suffer from renal failure as well as their families. *'74, 164 pp., 34 tables, $10.75*

A HANDBOOK OF URINALYSIS AND URINARY SEDIMENT *by* **Neil A. Kurtzman**, *Univ. of Illinois, Chicago, and* **Philip W. Rogers**, *Brooke Army General Hospital, Fort Sam Houston, Texas.* This handbook describes the common techniques of the clinical examination of urine, their interpretation, and the circumstances for which these techniques are of use. The microscopic examination of the urinary sediment is described in detail accompanied by color illustrations of the more common urinary formed elements. An emphasis on careful technique is combined with stress on both the uses and limitations of urinalysis as diagnostic tools. A chapter is devoted to the urine in disease where urinary findings in various renal and metabolic disorders are presented. Of value to students in particular as well as physicians, this book is designed to be a reference source of information concerning the clinical use of urinalysis. *'74, 112 pp., 28 il. in full color, 2 tables, $8.50*

THE UROLOGICAL MANAGEMENT OF THE PATIENT FOLLOWING SPINAL CORD INJURY *by* **John W. Pearman** *and* **Ernest J. England**, *both of the Royal Perth Hospital, Perth, Western Australia. Foreword by* **G. M. Bedbrook.** This monograph clearly shows that urinary tract infection is not the inevitable concomitant of the paraplegic state. It describes in detail the method of conservative management which enables most cases of spinal cord injury to develop satisfactory compensatory mechanisms of bladder emptying and remain free from urinary tract infection. Techniques of intermittent catheterization are described fully with the aid of many photographs. Six case histories along with x-rays are used to illustrate the indications for the various interventions and the results which can be achieved by them. The role of urinary diversion in patients following spinal cord injury is outlined. *'73, 304 pp., 78 il., 22 tables, $15.50*

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Studies in depth

Amoxil compared with ampicillin

When Amoxil was first introduced to the Medical Profession in May 1972 it was hailed as the successor to ampicillin. Since then research teams and clinical trial workers all over the world have reported that Amoxil is superior to ampicillin. Some of their reports have been in areas which were anticipated, but others have confirmed important superiorities which could not be predicted. These reports are obviously of considerable interest to the discerning clinician, and inevitably there have been many requests for a compendium of the available work. This is now available and will be sent upon request to interested clinicians. Brief summaries of the main areas considered in the compendium are given below.

More effective than ampicillin

There is evidence that Amoxil is more effective than ampicillin and this is particularly well illustrated in respiratory infections. Indeed, some reports have confirmed that Amoxil can succeed where ampicillin has failed[1,2,3]

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Early reports confirmed that Amoxil is twice as well absorbed as ampicillin, giving a peak serum concentration of 5.3 μg/ml[4] as opposed to ampicillin's 2.3 μg/ml[5]. Further work has shown that if both drugs are taken in the non-fasting state the overall absorption of Amoxil over the following 6 hour period is not significantly reduced, whereas that of ampicillin is reduced by nearly a third.

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Studies at the Brompton Hospital[6] have shown that whereas ampicillin penetrates well into purulent sputum it penetrates very poorly into mucoid sputum. These workers have shown that Amoxil penetrates equally well into both purulent and mucoid sputum, and suggest that this may have far-reaching consequences in the treatment of respiratory infections.

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Although ampicillin is generally well tolerated, rashes and diarrhoea can be an irritating nuisance. A review of published literature indicates that Amoxil produces substantially less rash and diarrhoea than ampicillin.

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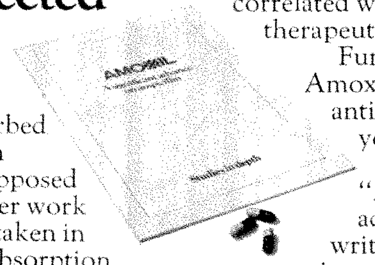
An ingenious series of experimental infections in mice has demonstrated that Amoxil exerts "... a more rapid bactericidal effect than ampicillin and this could be correlated with the difference in therapeutic effect."[7]



Further studies comparing Amoxil in depth with other leading antibiotics are in preparation. If you would like to receive a copy of the booklet "Amoxil – a significant advance on ampicillin" please write to the Freepost address given below. No stamp is required.

AMOXIL

Better than ampicillin in practice.

References: (1) Brit. J. Dis. Chest., (1972), 66, 185. (2) S.A. med. J., (1973), 47, 717. (3) Chemotherapy, (1973), 18, (Suppl.), 19. (4) Brit. med. J., (1972), 3, 13. (5) Antimicrobial Agents and Chemotherapy (1970), 438. (6) To be published (7) Antimicrobial Agents and Chemotherapy, (1970), 416.

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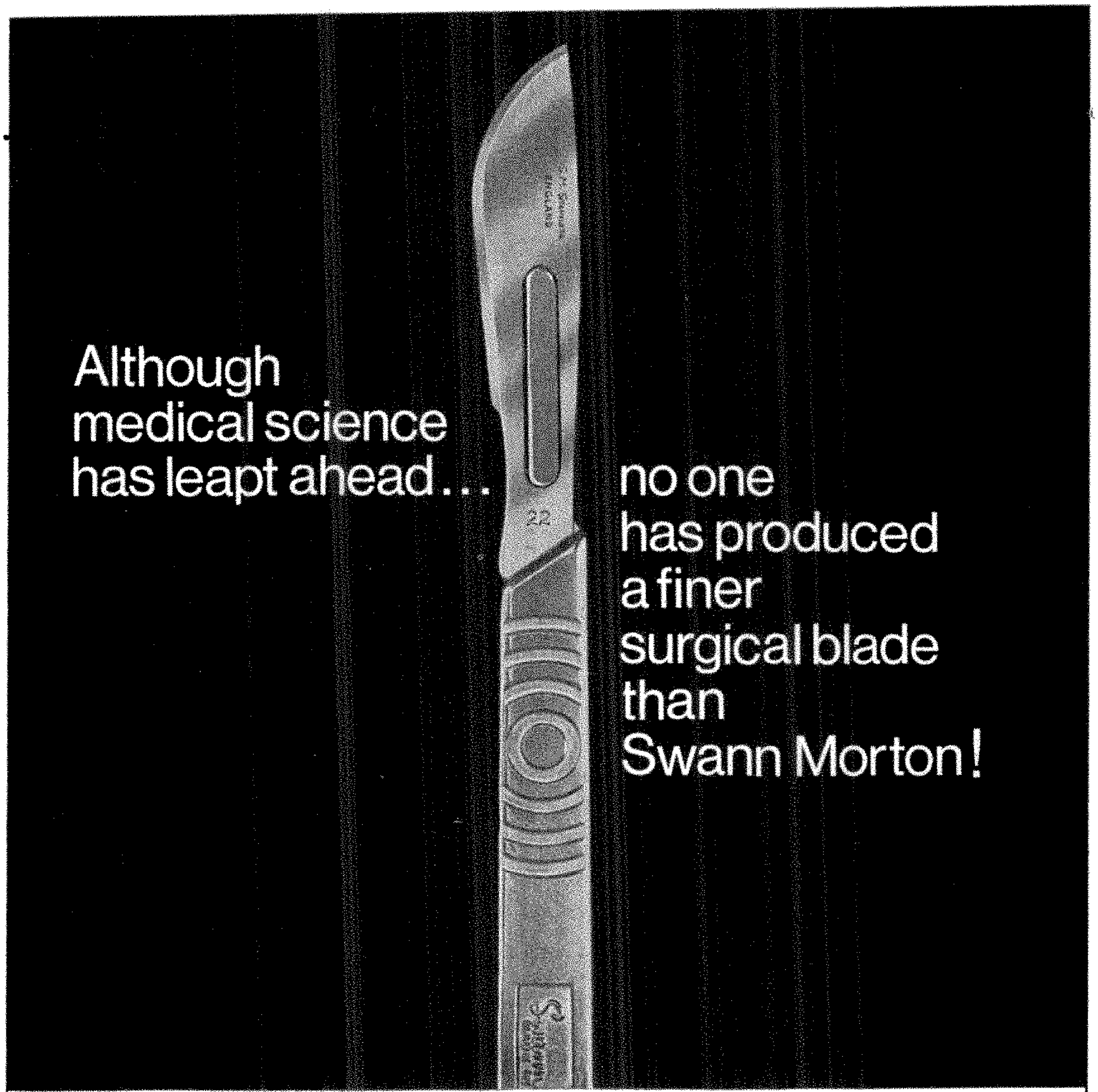

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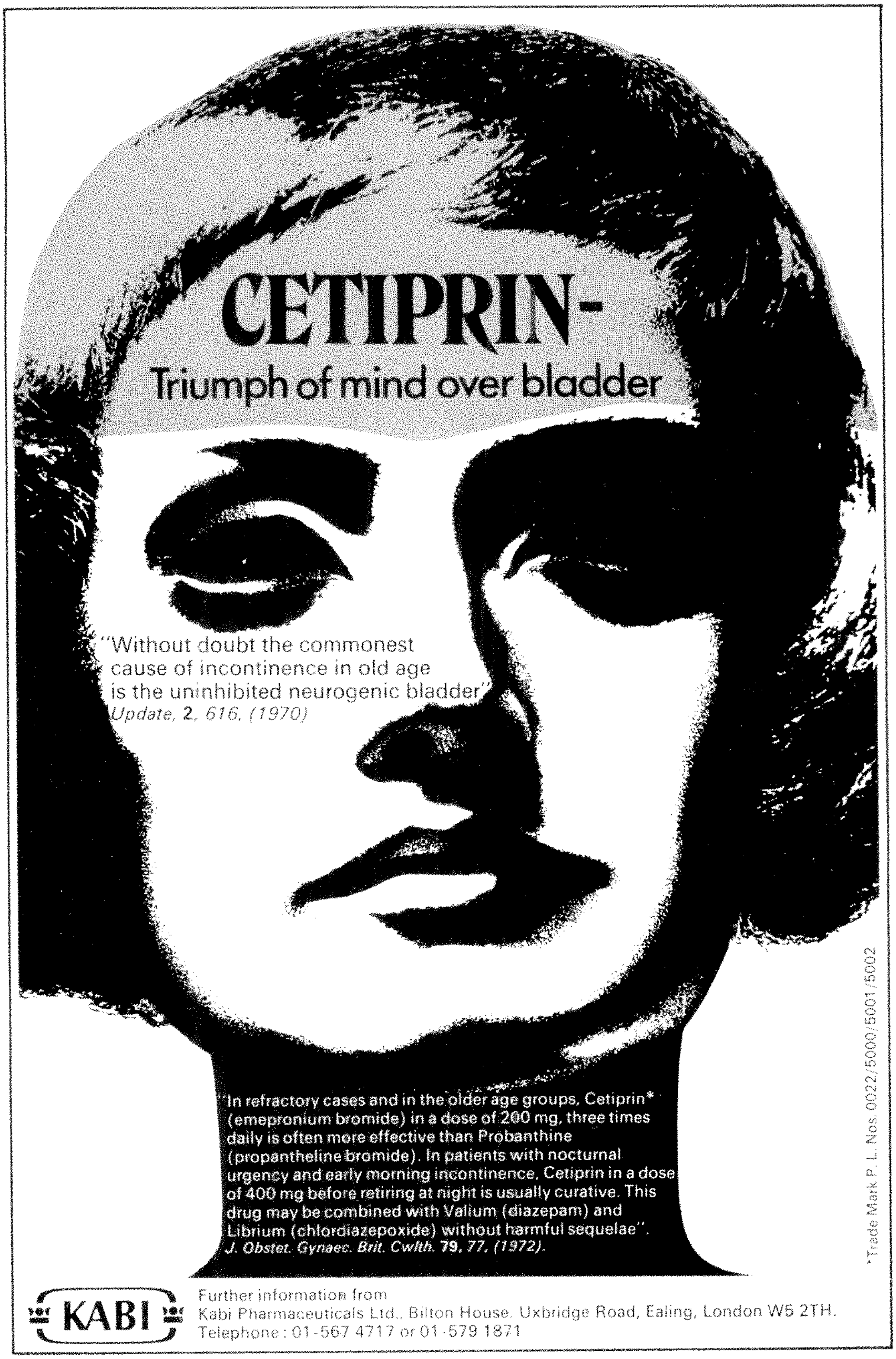

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British Journal of Urology (1974), **46**, 591-600

The Measurement of Individual Renal Plasma Flows using ^{123}I-Hippuran and the Gamma Camera

G. D. CHISHOLM, M. D. SHORT and H. I. GLASS

The Urology Unit, Department of Surgery, and Department of Medical Physics, Hammersmith Hospital, Royal Postgraduate Medical School, London

In the study of renal function by radionuclides, the uptake and excretion time curves of iodine-labelled orthoiodohippurate (Hippuran) have been subjected to a variety of analyses and interpretation. These curves, or renograms, have been interpreted in various ways, *e.g.* as indices (Tauxe, Hunt and Burbank, 1962; Wax and McDonald, 1964; Sherwood, Freeman and Joekes, 1964), as clearance values (Meschan *et al.*, 1966) and as estimates of renal blood flow (Taplin, Dore and Johnson, 1963). Computer-simulated renograms have been studied experimentally and clinically (Horgan *et al.*, 1967; Johnston and Kathel, 1972) while quantitation of renal plasma flow has been achieved using the isolated perfused canine kidney (Chisholm, Kulatilake and Evans, 1967).

Renal function studies using the gamma camera have also been reported. An early method involved electronic "splitting" of the gamma camera field and recording the count rate from each half on a dual channel recorder (Burke and Halko, 1967). Later techniques include an analogue method for selecting regions of interest in the gamma camera field (Constable and Werry, 1972) and a measurement of individual function using a simple ratio of counts due to ^{131}I-Hippuran within the kidney areas (Schlegel and Bakule, 1970; Hayes, Brosman and Taplin, 1974).

The clearance of Hippuran by the functioning (or effective) renal parenchyma represents the effective renal plasma flow (E.R.P.F.); a method has been described for the measurement of E.R.P.F. using a single injection of ^{125}I-Hippuran (Ram, Evans and Chisholm, 1968). We have extended that method to measure total and individual E.R.P.F. using the gamma camera and ^{123}I-Hippuran (Short *et al.*, 1973). This report presents the results of the clinical application of this method.

Materials and Methods

A gamma camera (Nuclear Enterprises MK III) was used to detect the administered radioactivity and data were recorded on computer compatible magnetic tape (Vernon and Glass, 1971).

The method used for data analysis has been reported elsewhere (Holroyd and Jones, 1969; Holroyd, Chisholm and Glass, 1970). The computer programmes were written in Fortran for use with a CDC 6600 computer (Vernon and Glass, 1971). The measurement of total E.R.P.F. from a non-renal area within the gamma camera field has been reported (Short *et al.*, 1973).

The majority of patients, especially the obese, were given 40 μCi ^{197}Hg-chlormerodrin 3 hours before the study in order to locate the kidneys precisely. There was no other preparation of the patient, who was normally hydrated at the time of the test. With the patient in the prone position, the gamma camera was lowered as close as possible to the skin and the precise position of the kidneys was established from the ^{197}Hg-chlormerodrin image. The image of the kidneys was

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

Table I

Values for E.R.P.F. and the Proportion to each Kidney in 16 Patients with Normal Renal Function (Group 1).

	Mean	Range
Total E.R.P.F. (ml/min)	381	216-695
Left kidney (%)	50	44-60
Right kidney (%)	50	40-56

Table II

Clinical Details and Values for E.R.P.F. and the Proportion to each Kidney in 25 Patients with Renal Disease (Normal Blood Urea)

	Patient	Age	Diagnosis	Total E.R.P.F. (ml/min)	Left kidney (%)	Right kidney (%)
1.	H. B.	65	Obstructed ureters: prostatic hypertrophy	670	61	39
2.	W. C.	33	Obstructed R. ureter: carcinoma rectum	247	95	5
3.	S. S.	40	R. calculous pyelonephritis	319	88	12
4.	V. W.	39	L. calculous pyelonephritis and previous L. partial nephrectomy	294	32	68
5.	H. F.	63	Obstructed ureters: prostatic hypertrophy	148	42	58
6.	A. C.	43	L. calculous pyelonephritis and hydronephrosis	224	27	73
7.	T. B.	67	I.V.P.—unequal excretion. Prostatic hypertrophy	212	66	34
8.	B. R.	60	L. hydronephrosis	452	10	90
9.	J. M.	48	L. renal artery stenosis	326	21	79
10.	F. J.	56	R. calculous pyelonephritis	435	60	40
11.	A. H.	71	L. staghorn calculus, R. hydronephrosis	110	50	50
12.	G. P.	71	Obstructed ureter: L. hydronephrosis	176	43	57
13.	J. G.	43	Hypertension. Small pyelonephritic R. kidney	375	65	35
14.	H. L.	76	R. renal cell carcinoma	346	88	12
15.	A. S.	74	R. hydronephrosis	281	92	8
16.	G. E.	23	L. hydronephrosis	575	19	81
17.	R. C.	53	Bilateral renal calculi	215	5	95
18.	C. C.	55	L. hydronephrosis	186	26	74
19.	K. M.	15	R. hydronephrosis	290	67	33
20.	P. P.	30	L. hydronephrosis	195	38	62
21.	S. H.	55	R. renal calculi and hydronephrosis	379	61	39
22.	S. S.	35	L. hydronephrosis	435	21	79
23.	A. B.	36	L. hydronephrosis	663	4	96
24.	A. B.	62	Obstructed ureters—urinary diversion	500	0	100
25.	D. M.	45	Renal artery stenosis	563	0	100

positioned in the lower portion of the gamma camera field of view to facilitate the selection of a tissue background region. 400 μCi of ^{123}I-Hippuran was injected into an antecubital vein and the data were recorded on magnetic tape from the time of injection. The recording was continued for 20 minutes and a 5 ml venous blood sample was taken about 15 min after injection.

Radiation Dosimetry

Renography with ^{131}I-Hippuran and the gamma camera, using acceptable diagnostic dosages, provides an insufficient count rate for quantitative studies owing to the limited sensitivity of the collimated gamma camera. This problem was overcome by the use of ^{123}I-Hippuran[1]; the physical half-life of ^{123}I is 13 hours. The radiation dose to kidneys with normal function has been calculated to be 0·07 m rads/μCi, which is only one-fifth of the dose obtained with ^{131}I-Hippuran (Short *et al.*, 1973). This reduced radiation dose is particularly important for serial studies in the same patients and for studies in patients with abnormal renal function.

---

[1] Supplied by the M.R.C. Cyclotron Unit, Hammersmith Hospital.

Patients

50 adult, non-pregnant, patients were selected for study. In Group 1, 16 patients had equal function as judged by the excretion pyelogram and had normal blood urea levels; the age range was 37 to 75 years. In Group 2, 25 patients had unequal renal function due either to unilateral or bilateral renal disease; the blood urea was normal. In Group 3, 9 patients had renal disease with blood urea values between 82 and 297 mg%.

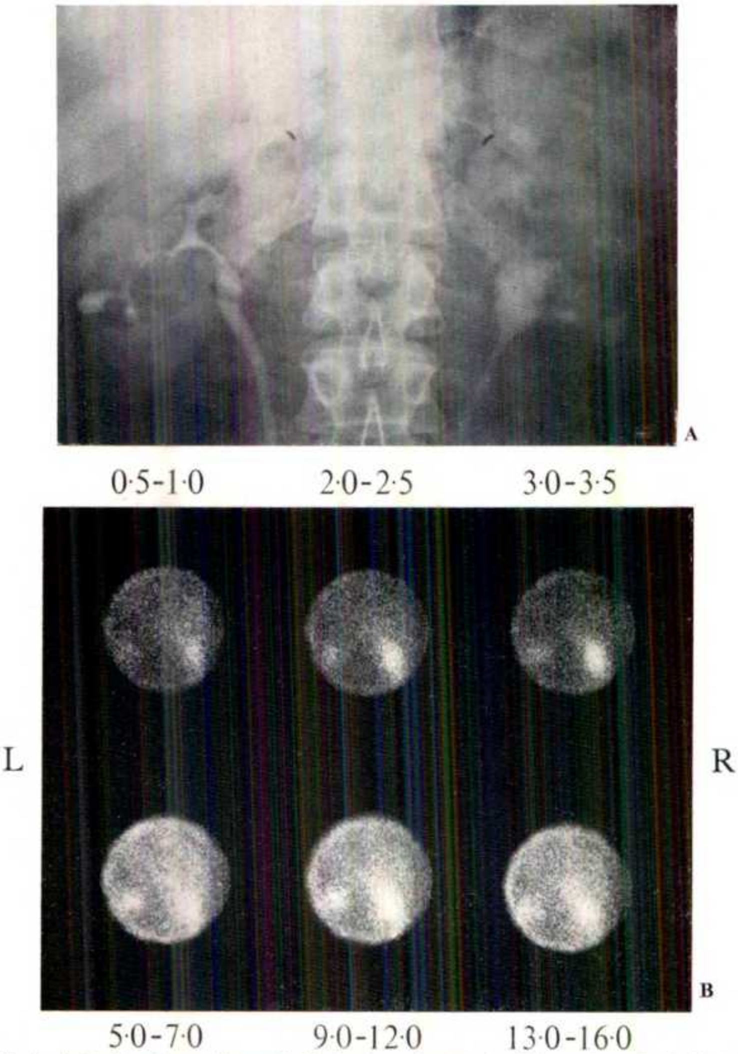

Fig. 1. Patient R. C. Aged 53. Blood urea 36 mg%. Under investigation for bilateral renal calculi. **A,** Excretion urogram at 10 min, showing bilateral pyelonephritis with small left kidney. **B,** Serial scintiscans. The sequence shows the poor isotope uptake by the left kidney. The figures indicate the time, in minutes, following the injection. *Note*: these pictures are taken from the back, *i.e.* the reverse of the urogram.

Results

All of the patients in Group 1 were considered to have normal renal function as demonstrated by excretion urography and routine biochemical tests. The values for total E.R.P.F. (uncorrected for surface area) and the proportion of that flow to each kidney are summarised in Table I.

In Group 2, where there was asymmetrical renal function with normal blood urea, the uncorrected E.R.P.F. ranged from 110 to 670 ml/min. The detailed results are given in Table II and an example of serial scintiscans, computer printout and uptake curves in Figure 1.

The results for uraemic patients in Group 3 are given in Table III and an example is illustrated in Figure 2.

Discussion

One of the principal limitations in the measurement of individual renal function has been the availability of invasive methods only. Not only does this restrict their use but it is also evident

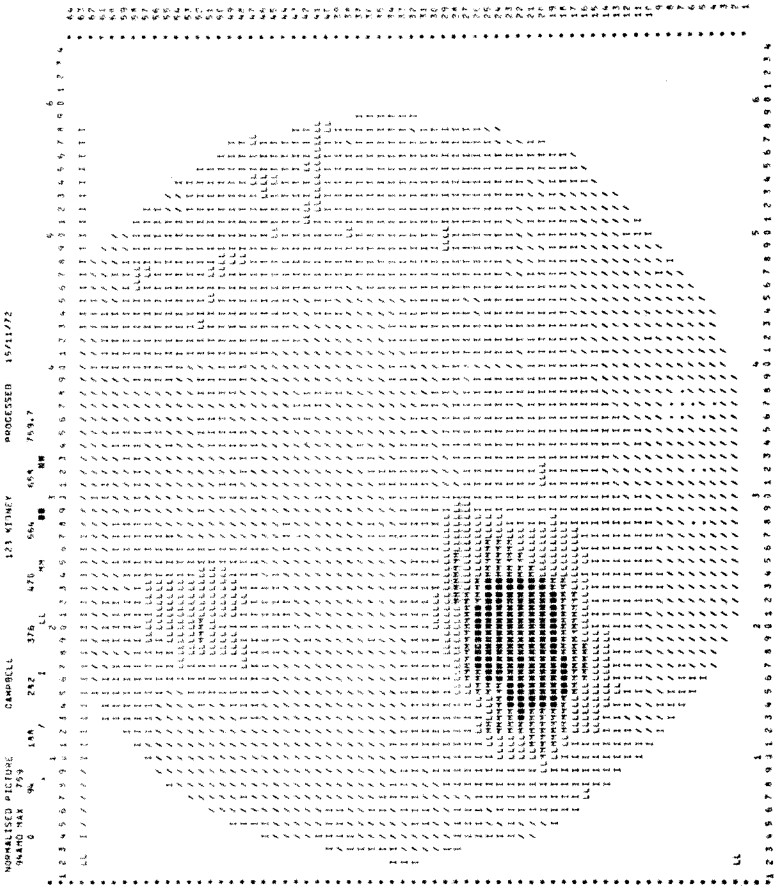

Fig. 1. C, Computer printout (corrected for camera uniformity) showing the total counts accumulated during the study.

that with a method such as bilateral ureteric catheterisation there may be technical problems as well as a significant morbidity. Radio-isotope renography offers a non-invasive method for assessing renal function and, by using a background subtraction technique, a measure of renal blood flow can be obtained (Britton and Brown, 1968, 1971; Short, Glass and Vernon, 1970). In practice, renography is used for a simple non-quantitative assessment of renal function. However, the popularity of renography has waxed and waned largely because it is only supplementary to existing techniques and, in its usual form, does not give precise enough information when this might be of value.

In this report we have described our experience with 50 patients using a method for measuring individual effective renal plasma flows (E.R.P.F.) by the gamma camera. This procedure requires no special preparation and has proved to be simple for the patient; it involves specialised equipment, but this is now available in most large centres.

This method also requires the availability of a suitable radio-isotope. We chose to study renal blood flow, rather than glomerular filtration rate, because Hippuran labelled with ^{123}I was available. The radiation dose due to ^{131}I-Hippuran is a major restriction to serial studies with the gamma

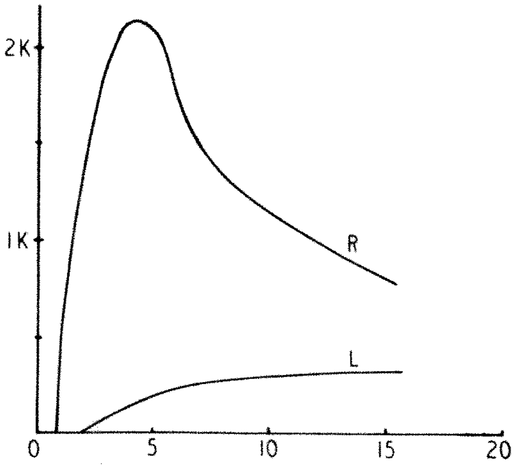

Fig. 1. D, Uptake curves after blood background subtraction. Proportional E.R.P.F. calculated from these curves—left 5%, right 95%. (Total E.R.P.F. from blood disappearance curve—215 ml/min.)

Table III

Clinical Details and Values for E.R.P.F. and the Proportion to each Kidney in 9 Patients with Bilateral Renal Disease and Uraemia (Group 3)

	Patient	Age	Diagnosis	Blood urea (mg%)	Total E.R.P.F. (ml/min)	Left kidney(%)	Right kidney(%)
1.	A. S.	83	Obstructed ureters: carcinoma prostate	297	32	30	70
2.	D. R.	19	Chronic pyelonephritis	170	85	23	77
3.	A. P.	81	Obstructed L. ureter: carcinoma bladder	82	112	10	90
4.	T. B.	70	Hypertension. Small R. kidney	110	101	95	5
5.	B. T.	38	Chronic pyelonephritis, ? solitary kidney	100	121	—	100
6.	J. C.	29	Chronic (reflux) pyelonephritis	136	104	50	50
7.	T. R.	57	Obstructed ureters: carcinoma prostate	120	95	38	62
8.	W. S.	65	Obstructed ureters: carcinoma bladder	234	81	53	47
9.	J. B.	55	Calculous pyelonephritis	180	150	0	100

camera (in the U.K.) so that it is preferable to use ^{123}I-Hippuran for these studies. In addition, the use of 500 μCi of ^{123}I-Hippuran instead of 100 μCi of ^{131}I-Hippuran (which gives a comparable radiation dose) increases the count rate by a factor of approximately 20 due to improved sensitivity of the gamma camera at the lower gamma-ray energy of ^{123}I. Normal count rates of 1500 to 2000 per sec for the whole field of view are obtained.

The use of a ^{197}Hg-chlormerodrin dose for precise kidney location was principally to ensure that the kidneys were positioned in the lower part of the gamma camera field, thus enabling an upper area to be used for the blood disappearance curve. Our results confirmed that this was the most convenient area for this measurement. In general, a kidney-locating dose of chlormerodrin should not be necessary except when the configuration of the patient creates a problem.

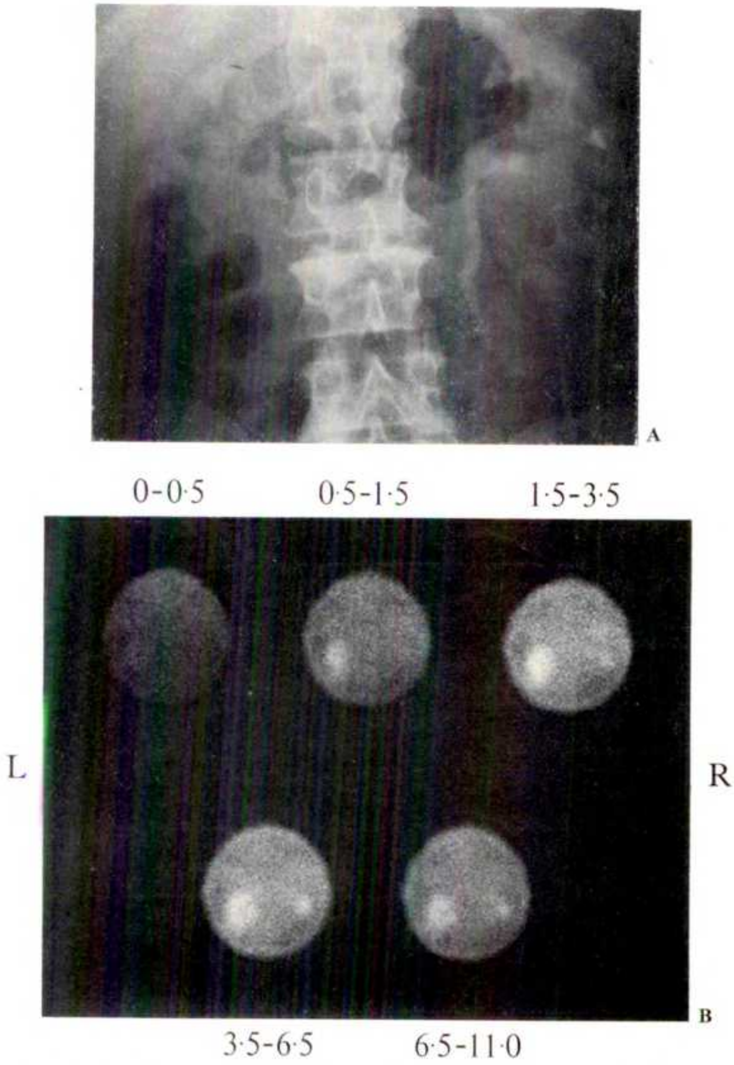

Fig. 2. Patient T. B. Aged 70. Blood urea 110 mg%. Under treatment for hypertension. A, Excretion urogram at 2 min, showing small right kidney. B, Serial scintiscans. The sequence shows delayed poor uptake by the right kidney. The figures indicate the time, in minutes, following the injection.

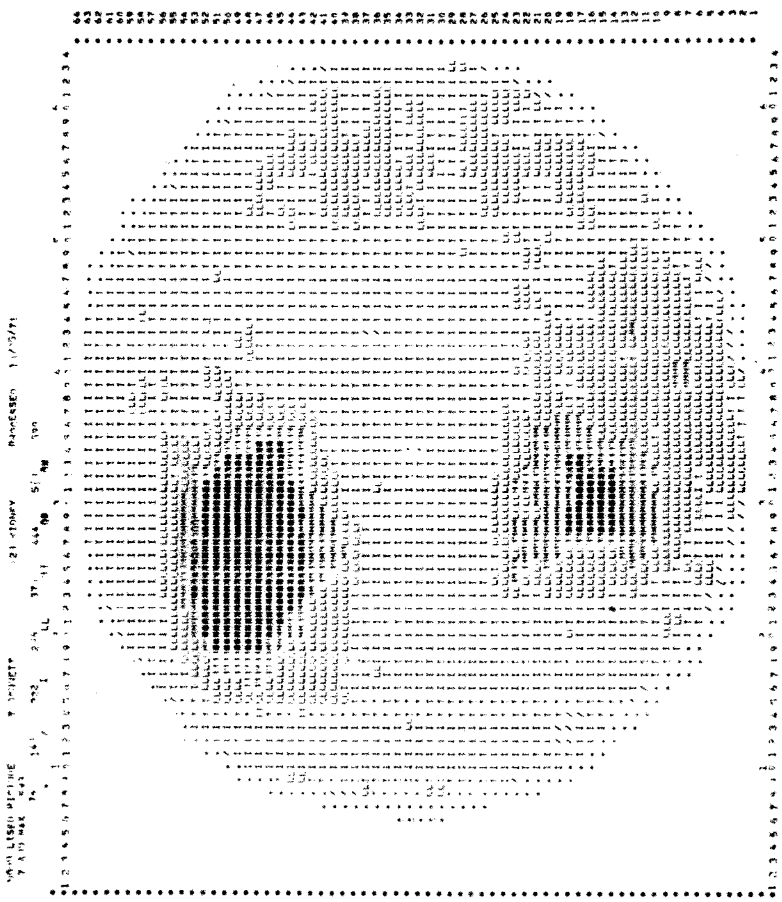

Fig. 2. C, Computer printout (corrected for camera uniformity) showing the total counts accumulated during the study. Activity around right kidney is due to uptake by the liver.

We have not attempted to compare our data with divided renal blood flows determined by clearance techniques. Instead, we have used an inferred comparison of E.R.P.F. from previous para-amino hippurate studies and the E.R.P.F. measured with the gamma camera (Short *et al.*, 1973).

The clinical value of this technique has been in 2 main groups of patients: (*a*) those with asymmetrical renal function and (*b*) those requiring serial measurement of renal function.

In assessing asymmetrical renal function, the clinician is dependent upon the interpretation of excretion urography together with biochemical tests. There are, however, occasions when more precise information about the function of each kidney could influence the management of a patient. For example, in renal calculus disease the decision to carry out either a nephrectomy or a conservative procedure might be guided by accurate information about the proportional contribution by each kidney to the total renal function.

In contrast, the results in this study suggested that a measure of E.R.P.F. in the presence of obstruction could mislead especially in acute or sub-acute obstruction where the low values gave no indication of renal reserve. Indeed, other predictive tests of recovery after the relief of an obstruction have also proved unreliable and it would appear that recoverability is still best assessed in retrospect, after the relief of the obstruction (Chisholm, 1974).

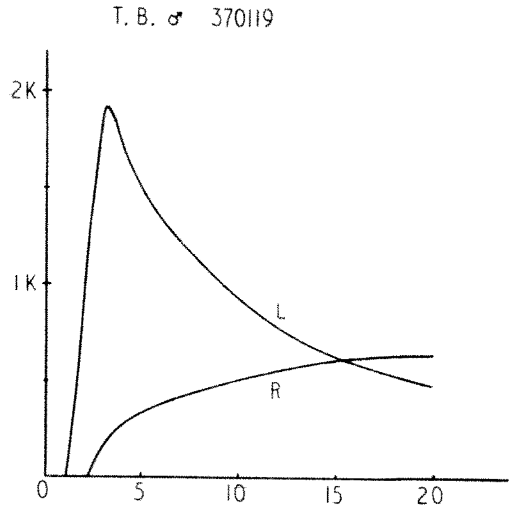

Fig. 2. D, Uptake curves after blood background subtraction. Proportional E.R.P.F. calculated from these curves—left 95%, right 5%. (Total E.R.P.F. from blood disappearance curve—101 ml/min.)

The investigation of asymmetrical renal function in the presence of hypertension has undergone a considerable change in emphasis during the past decade. Earlier enthusiasm for divided renal function studies by ureteric catheterisation has been dampened by difficulties with the technique and with interpretation of the results. The measurement of renal vein renin may prove to be a more reliable guide to unilateral renal disease causing hypertension, especially when the test is combined with methods for stimulating renin secretion. However, it is also recognised that an absolute measure of renal function is important since estimating the proportion from pyelography can be misleading (*New England Journal of Medicine*, 1973). The gamma camera has been used to study experimental renal hypertension (Galen and Schlegel, 1973) and to screen hypertensive patients (Keane and Schlegel, 1972), but it is suggested that the present technique will provide data that are useful in the management of these patients.

The second group of patients in whom absolute measures of renal function have a potential value comprises those where serial measurement is required. While it has been evident from this study that a measure of asymmetrical renal function does not help in the initial assessment of obstruction, it is particularly suitable for serial follow-up measurement. This may be of value not only after the relief of an obstruction, but also after any form of conservative renal surgery and after renal trauma. The restrictions imposed on the use of radio-isotopes for repeated studies limit the usefulness of this technique to either several measurements initially (usually within 4 weeks) or an annual measurement for several years. The gamma camera can be used to detect renal artery thrombosis after renal transplantation, but the detection of more subtle changes in renal blood flow would require at least an alternate day test to be of clinical value.

A further area of potential value for this technique with the gamma camera lies in the study of intra-renal blood flow and renal transit time, *i.e.* the rate of transport of Hippuran through the kidney (Short *et al.*, 1973). In the past, this area of investigation has been restricted because of the lack of reliable non-invasive methods. Krypton (Thorburn *et al.*, 1963) or Xenon wash out methods (Blaufox *et al.*, 1970) have provided the basis for most studies. Xenon has been used with the gamma camera in a study of renal and intra-renal blood flow in cirrhosis of the liver (Kew *et al.*, 1971). There remains, however, little information either about intra-renal blood flow in other diseases or the rate of transport of drugs through the kidney when the circulation is undergoing change as in anaesthesia or shock.

Summary

An evaluation has been made of a method for measuring effective renal plasma flow to individual kidneys in 50 patients.

The method consists of a single injection of ^{123}I-Hippuran and data collection using the gamma camera; an absolute measure of E.R.P.F. is then determined for each kidney.

To assist in the assessment of poor renal function, an area within the gamma camera field of view was used to obtain a measure of the contribution due to radioactivity of non-renal tissue overlying the kidney.

This method for measuring individual E.R.P.F. is particularly useful in assessing asymmetrical renal disease and in the long-term follow-up of a damaged kidney. The possibilities for investigation of intra-renal blood flow are discussed.

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Renal Pain and Haematuria

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Haematuria and loin pain are symptoms commonly encountered in urological practice. In most cases the standard investigations result in a diagnosis being made and the treatment is straightforward. Occasionally, however, the diagnosis proves elusive and the patient is then in danger of enduring unnecessary operations; the removal of a kidney known to be bleeding, the straightening of a "kinked" ureter, or, if pain is the only feature, of being labelled as neurotic. In 1967, Little, Sloper and de Wardener described 3 such patients and suggested a possible aetiology involving abnormalities of the renal vasculature. Since 1968 we have observed 39 patients over the age of 14 (Table I) in whom the presenting symptoms were haematuria or loin pain, or both, and in whom the usual urinary tract investigations had failed to provide a diagnosis.

Table I

Presenting Symptoms of Patients Studied

	Total	Male	Female
Painless haematuria	19	15	4
Loin pain with haematuria	17	0	17
Loin pain without haematuria	3	0	3
	39	15	24

Clinical Features

Of the 39 cases, 24 were referred initially to a surgeon, usually in the Urological Clinic but occasionally to a general surgeon or a gynaecologist. Most of the remainder were referred to the Nephrological Clinic. In nearly all the patients who presented with loin pain a provisional diagnosis of renal colic due to a calculus had been made initially and indeed in most of these the pain was of a severity similar to that of renal colic. The loin pain was bilateral in two-thirds of the patients, unilateral in one-third. In none were frequency or dysuria prominent features nor were rigors encountered but a low-grade pyrexia would often accompany an attack. The usual duration of the pain was from a few hours to several days and the intervals between attacks varied from 2 or 3 weeks to several months, or longer.

The bleeding in those patients whose loin pain was accompanied by haematuria varied from the heavy to the microscopic. In several cases a cystoscopy during an attack showed blood emerging from the ureteric orifice on the side of the pain. As was shown in Table I, all the patients who experienced loin pain were females and all but 3 of these had noticed or were found to have haematuria.

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Where haematuria was the only feature, the pattern in many cases was that of the benign recurrent haematuria syndrome in childhood, the bleeding following exertion or in some cases an upper respiratory tract infection. In a few cases, however, the haematuria was persistent and unrelated to any demonstrable precipitating factor. It is interesting that 1 of the male patients who had haematuria almost every time he passed urine for 3 years now only passes blood after exertion.

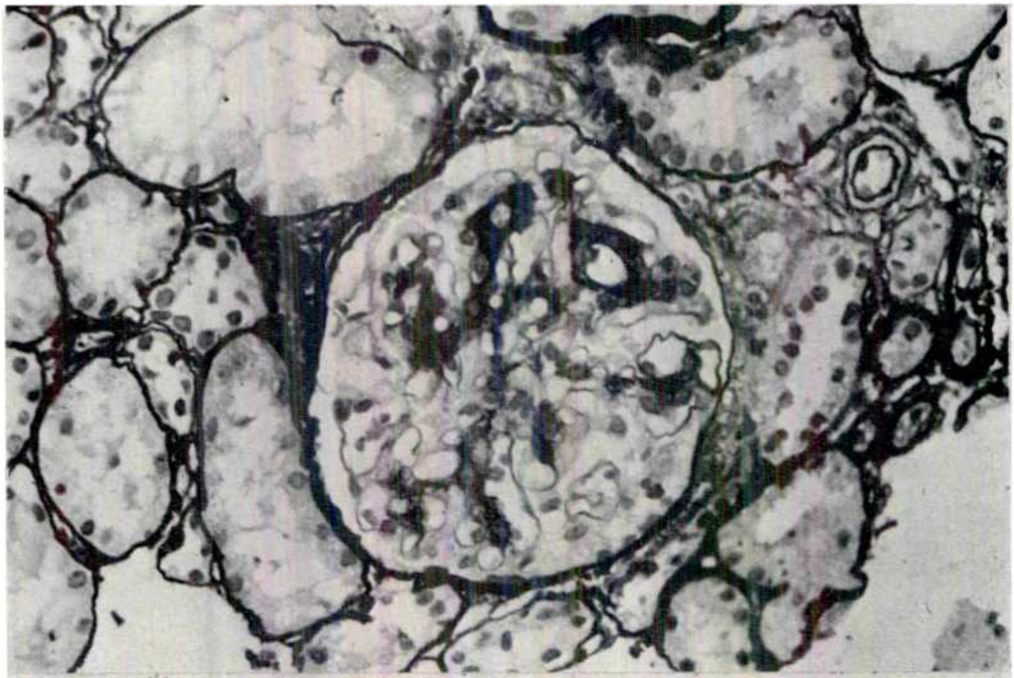
Investigations and Results

In all cases, we were of course particularly concerned to exclude the recognised causes of renal pain and haematuria. All patients had an intravenous pyelogram, if possible performed during an attack. All patients with haematuria (except the younger males) had a cystoscopy and if blood was seen emerging from a ureteric orifice, an ascending ureterogram and pyelogram were performed even though a previous I.V.P. had been normal. Many of the patients with persistent symptoms have had repeated I.V.P.'s and cystoscopies in order to be certain of detecting any abnormality which might emerge over the course of the disease. A careful drug history was taken in all cases with a view to picking out possible cases of papillary necrosis. Repeated urine cultures and cell counts performed in all cases both during and between attacks failed to reveal any cases of urinary infection.

Full urinary and serum biochemical investigations and tests of renal function were performed in all patients. The results were within normal limits nor was any deterioration in renal function noted in patients with longstanding symptoms. Abnormalities of calcium, urate, oxalate and cystine metabolism were excluded. Proteinuria often occurred during an attack of haematuria but usually disappeared between attacks. Prothrombin times were normal in all cases and there was no other evidence of a haemorrhagic diathesis in those patients in whom haematuria was a prominent feature.

Renal biopsy and bilateral selective renal angiography were performed in most cases. Renal biopsy was performed percutaneously using television monitored fluoroscopy (Boyd, 1974.) In patients with unilateral loin pain and in those with haematuria where blood had been seen emerging from one ureter on cystoscopy, the biopsy was taken from the affected side. Open renal biopsy was performed in only 2 cases, both early in the series when we had little experience in the diagnosis and management of the syndrome. Selective renal angiography was performed via femoral artery puncture using the Seldinger technique. In 6 patients blood was taken simultaneously from the brachial artery and renal vein for measurement of haemoglobin, platelet, fibrinogen and fibrinogen degradation products (F.D.P.). The results so far have shown a fall in platelet count and a rise in F.D.P. across the kidney during acute episodes in those patients with loin pain.

As has already been indicated, the routine bacteriological, biochemical, radiological and endoscopic investigations had failed to provide a diagnosis in any of these cases. However, on biopsy and selective renal angiography abnormalities were regularly present. Histologically, glomerular lesions were found consisting of mesangial proliferation and occasionally epithelial proliferation. Adhesions between glomerulus and capsule, with stalk thickening and pericapsular thickening were also regularly found (Figs. 1 and 2). Mild tubular damage consisting of irregularity or flattening of tubular epithelium with debris within the tubular lumen was noted commonly in those patients with loin pain but was not seen in those who had only haematuria. Vascular changes were rarely seen, but it must be stressed that the abnormalities which emerged as the result of the angiographic studies were in vessels larger than those which would be found in a cortical needle biopsy specimen. It may be significant that one of the two open biopsies demonstrated a larger vessel which showed deposition of fibrin on the intima with narrowing of the lumen.



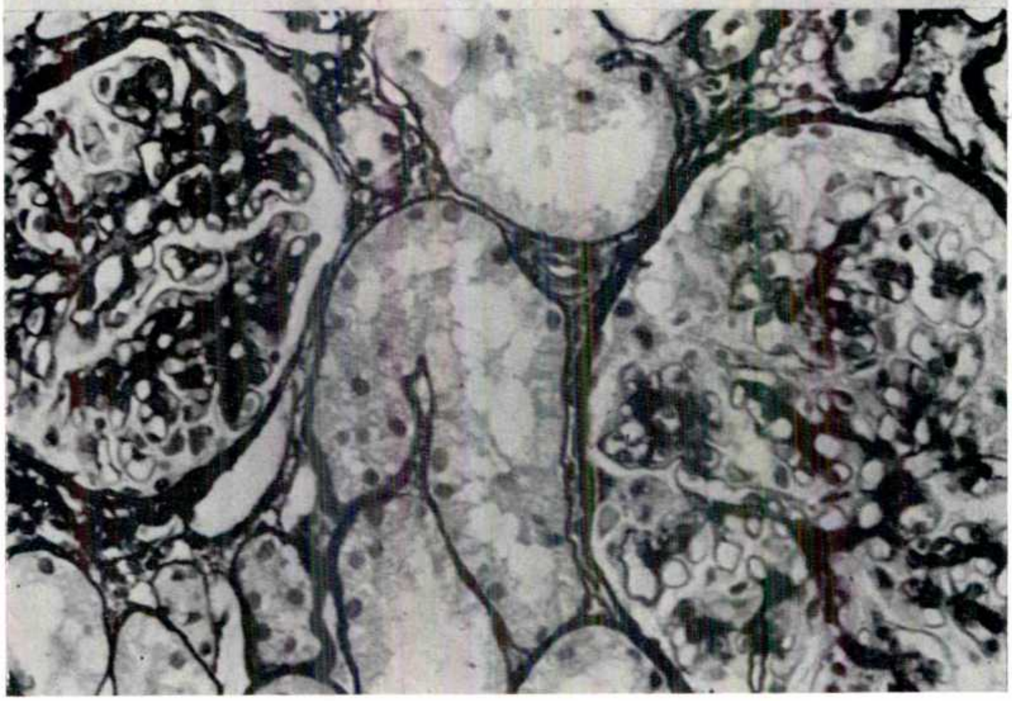


Fig. 1. Histological section of glomerulus showing segmental mesangial proliferation. Silver methenamine. × 1,000.

Fig. 2. Histological section of glomeruli showing pericapsular thickening and segmental mesangial proliferation. Silver methenamine. × 1,000.

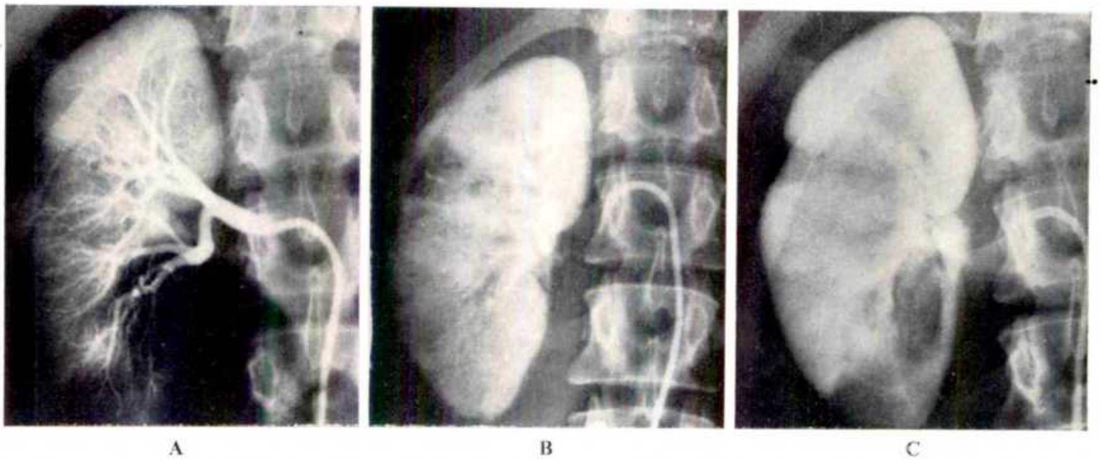


Fig. 3.A, Late arterial phase of selective renal angiogram showing complete occlusion of an interlobar artery and tortuosity and beading in many peripheral vessels.

Fig. 3.B, Nephrogram phase from the same series demonstrating stasis of contrast medium in the affected vessels.

Fig. 3.C, Nephrogram from a selective angiogram on the same kidney performed 6 months later showing a large renal infarct in the territory distal to the interlobar artery shown to be occluded in Fig. 3, A.

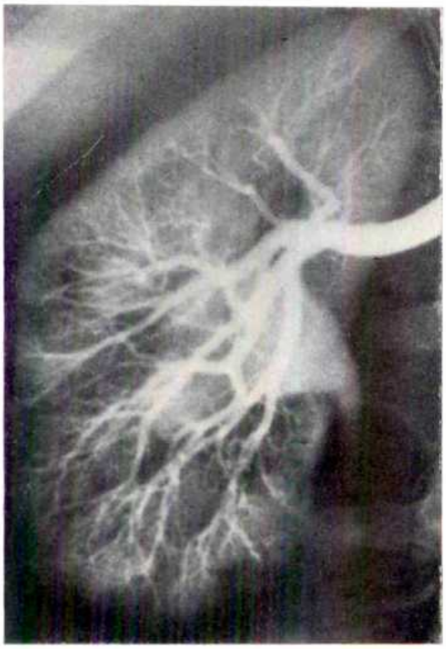


Fig. 4. Late arterial phase of selective arteriogram of right kidney showing widespread peripheral arterial disease. This is most obvious in the lower pole where corkscrew deformity of vessels and multiple areas of ischaemia can be seen.

Immunofluorescent studies were carried out on 16 renal biopsies. Mesangial deposition of IgG, IgA and B1C was a characteristic finding in the patients with painless haematuria whereas there was no detectable deposition of immunoglobulins or complement in either the mesangium or glomerular basement membrane in patients with loin pain and haematuria.

On selective angiography the main and segmental arteries showed no abnormalities. Most of the patients complaining only of haematuria were also found to have normal interlobar, arcuate and interlobular arteries. In contrast vascular abnormalities at this level occurred in all the patients with loin pain. The changes consisted of focal or widespread tortuosity, beading, stenosis or occlusion, abnormal bifurcation of arteries and stasis of contrast medium (Figs. 3, A, B, C and 4). In some cases ischaemic areas or scars were seen. These abnormalities were not necessarily confined to the side of the pain.

Discussion

It became clear during the course of this study that the patients with loin pain and haematuria formed a distinct group from those who had only haematuria (Fig. 5). Those with recurrent haematuria only were mostly male under the age of 20 and had similar clinical, histological and immunological features to those reported in children with the benign recurrent haematuria syndrome by Ross (1960), Berger (1969), Glasgow, Moncrieff and White (1970) and Roy *et al.* (1973). It was of particular interest to note that selective renal angiography failed to reveal any detectable abnormalities of the intrarenal vessels in this group of patients and despite the prolonged duration of the haematuria in some of these cases, none have shown any evidence of deterioration of renal function. It seems clear that, even where it is known which kidney is bleeding, surgery is contra-indicated, and that the haematuria will eventually cease, leaving no demonstrable diminution in renal function.

On the other hand, the loin pain group were all female, mostly over the age of 20 and although light microscopic appearances were similar in this group to those observed in the patients with painless haematuria, immunofluorescent studies revealed a marked difference in that there was no glomerular deposition of either immunoglobulins or complement. A further well-defined point of distinction between this group of patients and the former was the abnormalities of intrarenal vasculature which were clearly demonstrated by selective angiography. The aetiology

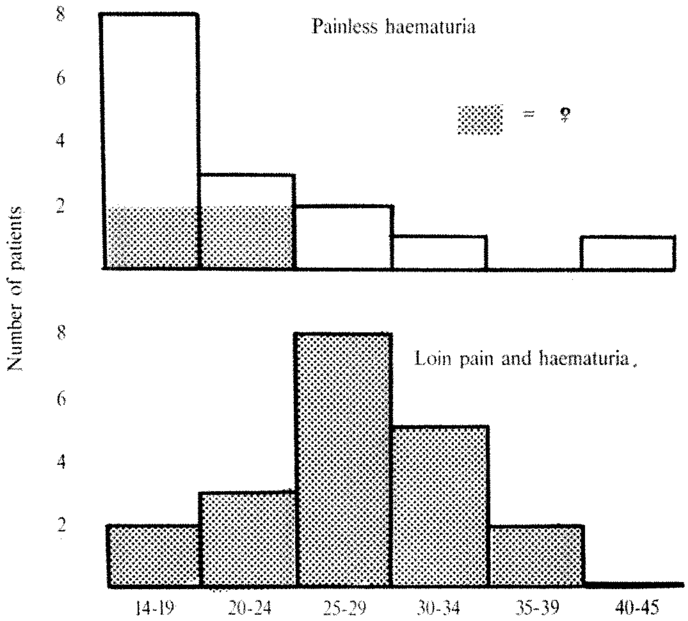


Fig. 5. Age at onset of symptoms.

Table II

Possible Pathogenesis of the Obstructive Vascular Changes

1. Atherosclerosis ± microemboli
2. Microemboli from other sources
3. "Vasculitis"
    (*a*) part of a generalised disease
    (*b*) involving the intrarenal vessels only
    (*c*) dysproteinaemias
4. Intravascular coagulation syndrome

of these changes is open to wide speculation (Table II). No patient has shown evidence of systemic arteritis, vascular disease elsewhere, nor a source of emboli. We feel that the most likely explanation is that a drug- or humoral-induced endothelial lesion resulting in the secondary formation of intrarenal microthrombi is the cause of the abnormalities observed. This appears to be accompanied by an increased transrenal consumption of platelets and fibrinogen. Oestrogens are known to induce changes in the coagulation system (Howie *et al.*, 1970) and to increase the susceptibility to thrombosis (Vessey and Doll, 1969) and in this context it is almost certainly relevant that all the patients in this group were female, many were taking the contraceptive pill at the time the symptoms commenced and most of these improved after ceasing to take the pill. One patient was of particular interest in that having had a hysterectomy and bilateral oophorectomy for endometriosis, she was given an oestrogen implant. Her attacks of loin pain started almost from the day of operation but began to diminish in severity 6 months later at a time when the implant would be expected to be losing its activity. Shortly afterwards the attacks ceased entirely and have not recurred.

Treatment is not easy. The pain is of sufficient severity that pethidine is often required for its relief and occurs with such frequency that the patients themselves and their doctors are reluctant to use potent analgesics in the quantities which would be necessary to give relief. Stripping of the renal pedicle at the time of open renal biopsy was used as a method of renal denervation in 2 patients and a third was subjected to an elective denervation in an attempt to control the pain. In 2 of these the relief of pain was complete for 6 months but the attacks of pain then returned as before. Microscopic haematuria persisted during the pain-free period. In the third, lasting relief of pain and haematuria has followed but since the patient ceased to take the contraceptive pill shortly after the operation, one cannot assess the effect of denervation in isolation in this case. Little, Sloper and de Wardener (1967) also noted only temporary relief of pain following renal denervation. Antibiotics in short and long courses have invariably been given before we see the patients, and as would be expected in a condition where there is no evidence of infection, no relief is experienced. As has already been mentioned, withdrawal of the pill may be effective, but if this is not successful or if the patient is not on the pill in the first place, treatment with anticoagulants seems to give the desired result. This was first started about 18 months ago when we had accumulated sufficient evidence to be reasonably sure of the cause of the syndrome and so far 8 patients have been treated for a mean period of 7 months with complete relief of their symptoms. Two patients who stopped anticoagulant therapy promptly suffered a return of their attacks of loin pain and haematuria but have since recommenced treatment, again successfully.

Summary

Extensive investigations have been performed on 39 adult patients suffering from renal pain or haematuria or both in whom the diagnosis was obscure.

The use of selective renal angiography and renal biopsy has shown that these patients fall into two well-defined groups. One of these, consisting largely of young males, showed no angiographic abnormality but the histological changes demonstrated were similar to those found in the benign recurrent haematuria syndrome of childhood. The other group, all of whom had severe loin pain and most of whom had haematuria, were found to have angiographic and other abnormalities suggesting a humorally induced microangiopathy.

In none of these patients is operation indicated despite the apparent "surgical" nature of their complaints. In the former group no treatment is necessary, in the latter group treatment with anticoagulants has given promising results.

Failure to recognise this condition may well result in the performance of unnecessary operations and ultimately the patient is likely to be labelled as a neurotic.

We would like to express our particular thanks to Dr Walter Boyd who performed most of the selective renal angiograms and to Dr Barbara Ockenden who has reported on the renal biopsies.

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Electron Microscopy of the Human Ureteric Innervation

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For more than a century, the control of ureteric function has been a much debated question. Despite extensive morphological and physiological studies, confusing and often conflicting opinions are proposed regarding the role played by the autonomic nervous system in the physiology of the ureter.

Ureteric motility was initially thought to be a purely myogenic phenomenon. Engelman's paper (1869) is the foundation of the myogenic theory of ureteric peristalsis. Later the pharmacological and electrophysiological works of Bozler (1938), Lapides (1948) and Kiil (1957) presented little evidence that disagreed with this initial theory. This concept was further documented by several authors who denied the possibility of neurogenic control because they could not demonstrate histologically nerve endings in the ureteric musculature (Engelmann, 1869; Disselhorst, 1894; Satani, 1919; Pieper, 1951 and Gosling, 1970). However, more recent physiological and pharmacological experiments have presented evidence that the ureter is under some nervous control (for review see Boyarsky and Labay, 1972). New specific neurohistochemical procedures have recently allowed the demonstration of a dual adrenergic and cholinergic innervation of the ureter (Elbadawi and Schenck, 1969; Schulman *et al.*, 1972). However, the limits of resolution of light microscopy make it difficult to interpret the precise relationship of individual ureteric nerves and smooth muscle cells, and makes it impossible to distinguish if a single nerve fibre contains acetylcholine and noradrenaline, or if two different fibres are closely related running in the same nerve bundle.

A new approach to this problem is made possible with the electron microscope. The increased resolution of electron microscopy allows one to study the precise relationship of terminal nerve fibres and smooth muscle cells and to follow the distribution of peripheral autonomic nerves at the ultrastructural level. Also, this method may be used to differentiate adrenergic from cholinergic nerves (see reviews by Grillo, 1966; Hökfelt, 1969 and Burnstock, 1970).

The recent electron microscopic studies of Taxi (1965) and Dixon and Gosling (1971) showed the existence of adrenergic and non-adrenergic nerves in the mammalian ureter. These studies were however confined to the upper segment of the ureter, renal pelvis and calyces and did not concern human material.

Only Notley (1968 and 1970a) has examined the innervation of the ureter in man but failed to distinguish between the different types of nerve terminals and did not observe ganglionic structure in the ureter.

Notley (1970*b*) and Libertino and Weiss (1972) studied the smooth musculature of the human ureter and showed close relationships between smooth muscle cells but could not demonstrate tight junctions (nexus) in the human ureteric musculature.

Material and Method

Our study concerns human material removed during operation (*e.g.* at cystectomy or nephrectomy).

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Tissues were fixed in 4% glutaraldehyde buffered with 0, 1 M phosphate buffer at pH 7·2 for 90 minutes and postfixed in 2% osmium tetroxide for 30 minutes. After fixation the tissues were dehydrated in ascending concentrations of ethanol and embedded in epoxy resin. Ultrathin sections were double stained with uranyl acetate and lead citrate and examined with a Siemens Elmiskop electron microscope.

Some specimens were incubated for 1 hour in a Krebs-Ringer solution containing 20 μg/ml of noradrenaline. Other tissues were incubated 30 minutes in a Krebs-Ringer solution containing 2 mg/ml of 5-hydroxydopamine (5-OH-DA). These specimens were fixed and prepared as described above for the untreated material.

Some specimens were fixed in 1% potassium permanganate at pH 7·4.

Results and Discussion

The present paper focuses on the main results of this investigation and discusses briefly their implications. In order to make our statement more evident, we will first examine the innervation of the ureteric musculature and consider afterwards the problem of ureterovesical ganglionic structures.

The Innervation of the Ureteric Smooth Musculature

The smooth muscle cells of the human ureter are approximately 300 to 400 mμ long and 4 to 7 mμ wide (in the nuclear area) (Fig. 1). The size and form of the cells depend on the state of contraction or relaxation of the musculature at the time of fixation of the specimen. So, contracted cells show numerous interdigitations and their nucleus and cell surface appear irregular (Fig. 2).

The major part of the cytoplasm is composed of myofilaments orientated in the direction of

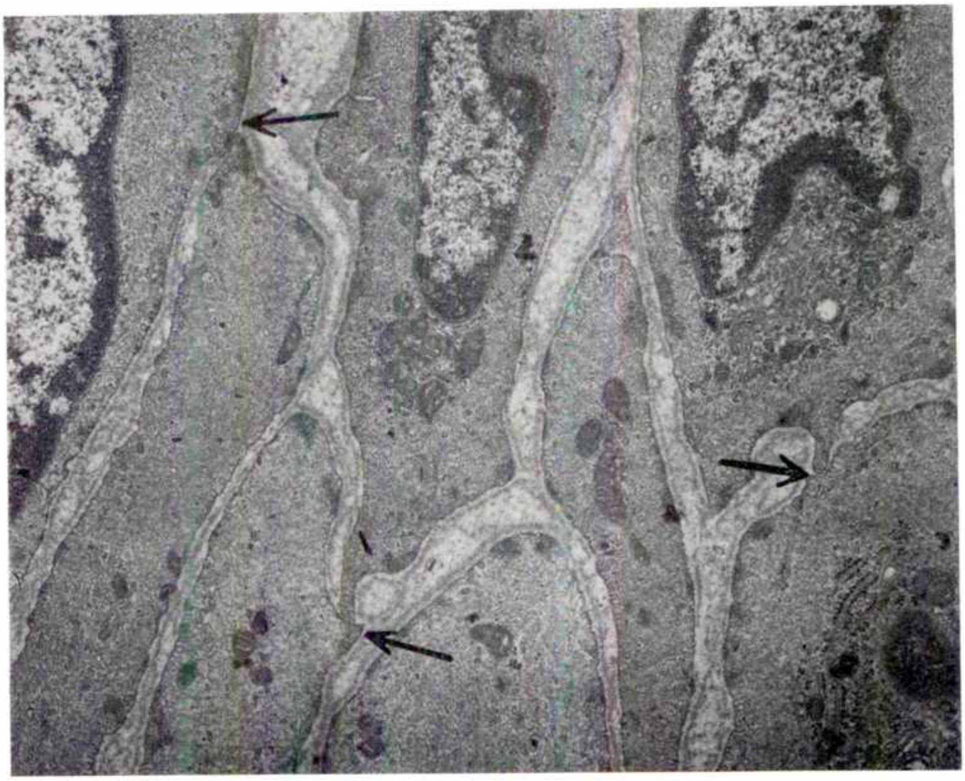


Fig. 1. Electron micrograph of human ureteric musculature. Each smooth muscle cell is surrounded by 4 to 6 other muscle cells interconnected to each other by numerous close contact-areas (arrows). × 18,400.

the long axis of the cell (Fig. 1). The mitochondria are orientated in the direction of the myofilaments and appear mainly at the nuclear poles as well as at the periphery of the cell near the plasmatic membrane. The cell membrane is invaginated by numerous micropinocytotic vesicles opening at the exterior of the cell and which markedly increase the extracellular space made of collagen and elastic fibres. This space is occupied by a net of capillary blood vessels and nerve bundles.

In the muscle bundles, each smooth muscle cell is surrounded by 4 to 6 other muscle cells. These cells are interconnected in numerous contact-areas (Fig. 1). The narrowest musculo-muscular connection is represented by a tight junction called a *nexus* (Dewey and Barr, 1964). The *nexus* constitutes a fusion area between the external lamellae of the cell membranes (Fig. 3). These fusion areas are observed particularly well after fixation with potassium permanganate (Dewey and Barr, 1964). Previous authors could not demonstrate nexuses in the human ureteric musculature most probably because their specimens were fixed in standard media (Notley, 1970*b*; Libertino and Weiss, 1972). It is now generally agreed that the nexus represents a pathway of lower electric resistance to the transmission of impulse from one muscle cell to another (Barr *et al.*, 1968). These musculo-muscular junctions represent an anatomical substrate allowing the ureteric musculature to be considered as an electric syncitium in which the contraction is transmitted from one muscle cell to another.

If the nexus constitutes the narrowest musculo-muscular connection which has been observed, there exist however other types of relationships between the smooth muscle cells. Hence, numerous protrusions are noted between the cells, giving the impression of a bridge (Fig. 4). Sometimes a cell forms a sort of diverticulum which deeply invaginates a neighbouring cell (Fig. 5). At this

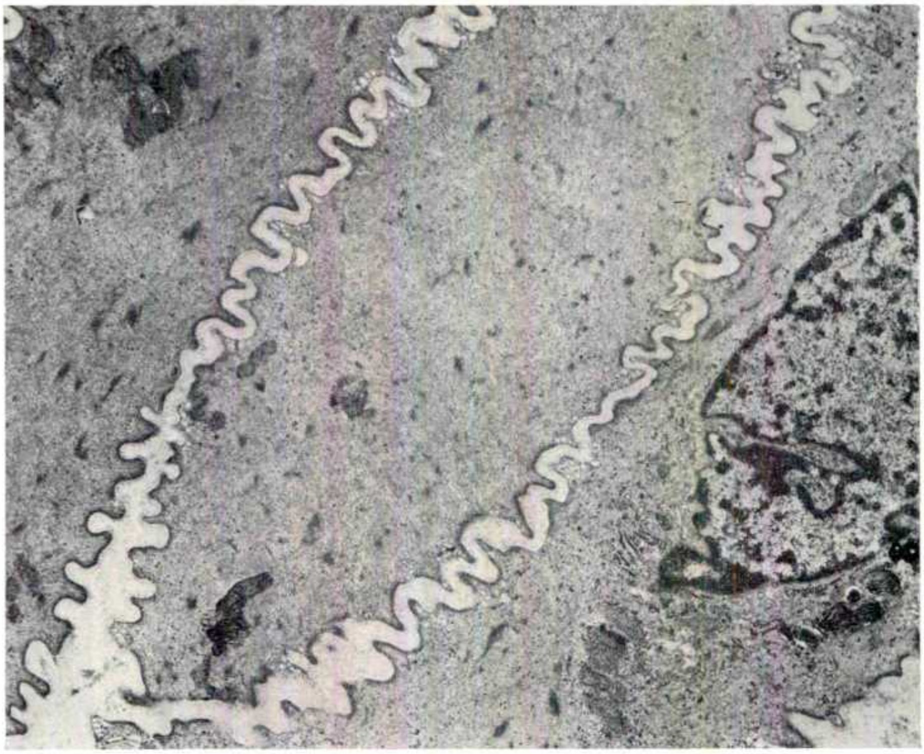
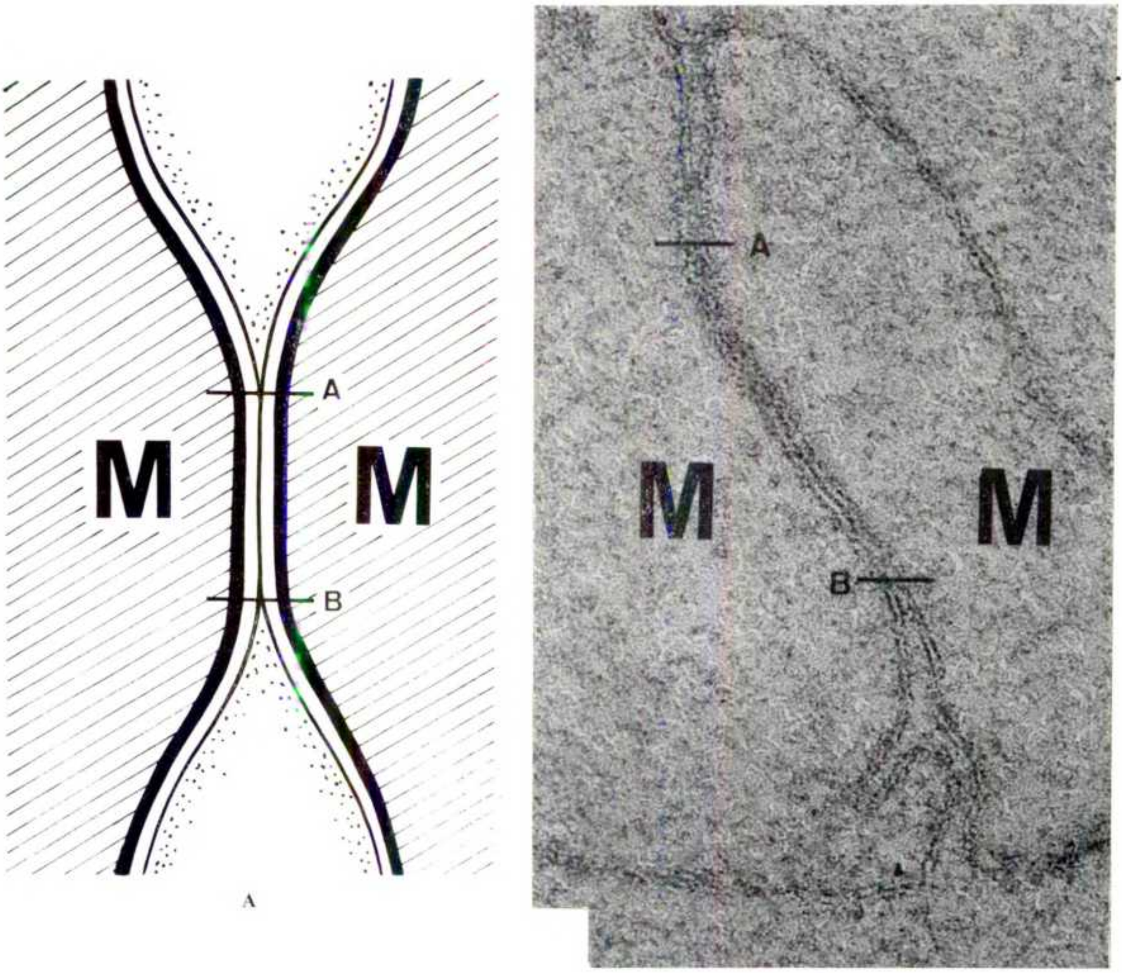


Fig. 2. During *contraction*, muscle cells show long interdigitations which are possible site of interactions between cells. These invaginations are spread over the whole cell cytoplasm and nucleus. × 10,000.



A

B

Fig. 3. A *nexus* between two smooth muscle cells. This fusion area of plasma membrane represents a low resistance pathway to the impulse transmission from one muscle cell to another. **A**, Diagrammatic representation of a nexus. **B**, Electron micrograph of human ureteric musculature fixed in potassium permanganate showing a nexus. × 200,000. **M**: muscle cell-A-B : nexus

level the intercellular space may be reduced to 100 Å, whereas it most frequently reaches about 200 Å to 300 Å. The protrusions are especially numerous when the musculature is contracted forming then a kind of interdigitation from one cell to another one (Fig. 2).

The nerve fibres are composed of a various number of axons. They are grouped in bundles which run in the different layers of the ureter (Fig. 6).

Large nerve trunks run in the outer connective tissue surrounding the muscle coat. Smaller nerve bundles ramify within the muscular layer and in the submucosa. Single axons are present along smooth muscle cells and in the subepithelial layer. Each axon shows beaded enlargements along its terminal course. These varicosities are filled with clusters of synaptic vesicles and mitochondria. It is primarily through the varicosities that the nerve fibres contact and may influence the effector smooth muscle cells (Burnstock, 1970).

Occasionally direct contacts between a nerve and a smooth muscle cell involving a membrane apposition with a narrow gap reduced to only 150 Å to 250 Å have been observed. At these

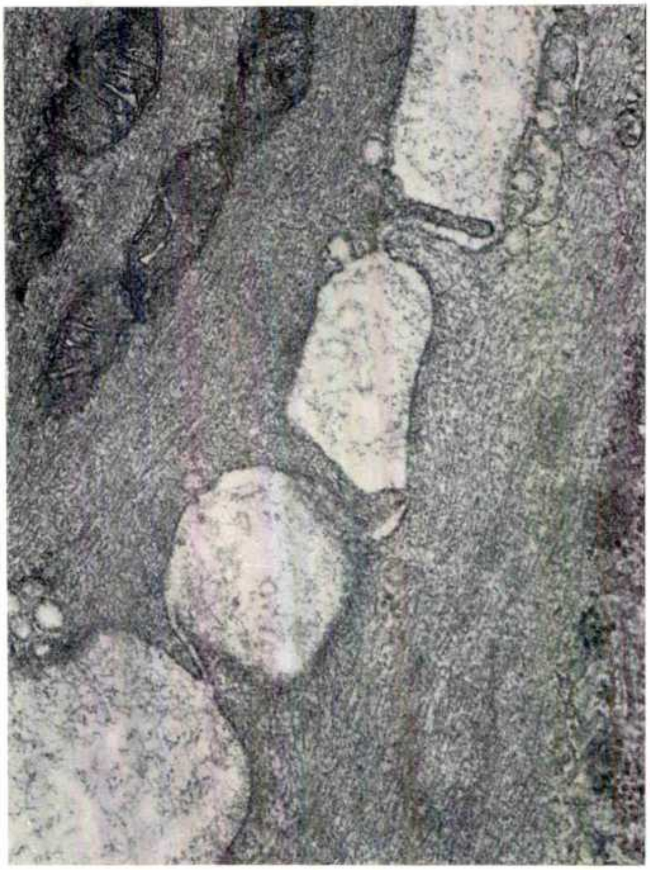


Fig. 4. Protrusions of adjacent muscle cells. These close contacts can sometimes give false impression of a bridge, there is no protoplasmic continuity but a narrow separation of 100 to 200 Å between the two cell membranes. × 36,000.

areas of contact the axon usually lies in a depression on the surface of the effector cell (Fig. 7). The contacting membranes lack specialisation but these neuromuscular junctions are considered as functional synapses (Taxi, 1965; Burnstock, 1970).

The very limited number of synapses observed in the ureter cannot sufficiently account for the transmission of a stimulus in the ureteric musculature. Therefore it should be assumed that they do not represent the only site where the excitor transmission can take place and, further, that the nerve fibres are susceptible of releasing from their varicosities, at other levels, a mediator acting at a distance on the muscle cells. Similar conclusions have been drawn in other types of smooth muscle (intestine, uterus) and in different species (see review by Burnstock, 1970).

Indirect contacts, in which a space of 500 Å to several thousand Angstroms was occupied by connective tissue elements interposed between terminal varicosities and smooth muscle cells were observed much more frequently in the ureter.

Two main types of nerve were recognised in the ureter. Identification was based on the fine structure of the synaptic vesicles contained in axonal enlargements at the nerve endings (Hökfelt, 1968, Burnstock and Iwayama, 1971). The *adrenergic* component is characterised by small granular vesicles (approximately 500 Å diameter) including an electron dense core which represents the site of storage of noradrenaline, the physiological adrenergic transmitter (Fig. 8).

The non-adrenergic type, considered to be the *cholinergic* component, is composed of small

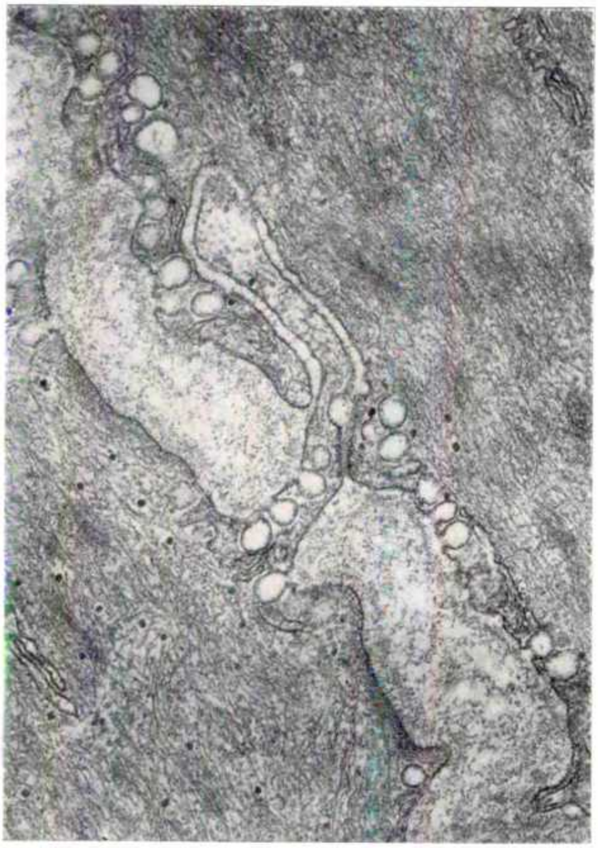


Fig. 5. Another type of intercellular relationship is represented by intrusion of a cytoplasmic process of muscle cell into a neighbour cell. × 32,000.

agranular (empty-looking) vesicles (Fig. 9). In both types of axons a few large granular vesicles (700 to 1300 Å diameter) and mitochondria are observed. These two types of nerve endings were encountered in the adventitia, muscular layer and submucosa of the ureter.

In some instances the electron dense granules were poorly preserved and adrenergic axons appeared hardly distinguishable from non-adrenergic nerves.

Incubation of specimens in a noradrenaline solution increased significantly the proportion of dense granules in synaptic vesicles of adrenergic nerves, whereas the vesicles of non-adrenergic (cholinergic) nerves remained empty (Fig. 10).

The identification of adrenergic and cholinergic nerves was further demonstrated with the aid of 5-*hydroxydopamine* (5-OH-DA), a "false" sympathetic neurotransmitter which has recently proved useful as a specific marker for adrenergic nerve endings in the peripheral sympathetic nervous system (Tranzer and Thoenen, 1967).

Treatment with 5-OH-DA aided significantly the identification of adrenergic nerves because of the important increase in electron dense granules induced in the adrenergic vesicles by the uptake of this osmiophilic "false" neurotransmitter (Schulman, 1974). Numerous axon profiles observed in the muscle layer and submucosa contained these heavily granulated vesicles (Fig. 10). However, cholinergic nerves appeared unchanged since they are not affected by treatment with 5-OH-DA (Tranzer *et al.*, 1969). The two kinds of axons may occur in pairs in close contact

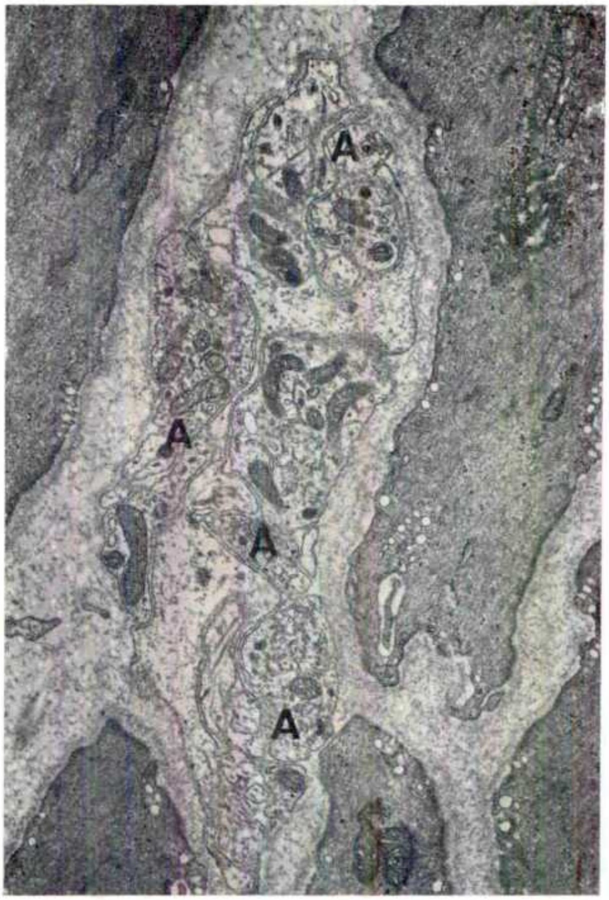


Fig. 6. A large nerve bundle, composed of 4 axons (A) is running between smooth muscle cells. × 18,400.

with each other in the same nerve fibre and this provides a morphological evidence for a possible interaction between adrenergic and cholinergic nerves in the ureter.

Cholinergic nerves have been considered as possible sensory nerve endings in various organs (Cauna *et al.*, 1969; Nadol *et al.*, 1970).

It has also been proposed that the adrenergic nerves may potentiate adjacent cholinergic sensory nerve endings (Ellison and Hibbs, 1973). The cholinergic innervation of the ureter appears quite important and it is suggested that cholinergic nerves may act as possible sensory stretch receptors.

Since Bozler's work (1941, 1948) smooth muscles were classified in two different groups: on the one hand, the unitary muscles such as those of the intestine, the uterus and the ureter, which are spontaneously active and in which the conduction occurs from muscle fibres to muscle fibres; on the other, the "multi-unitary" muscles, such as the nictitating membrane, the iris sphincter, the bladder and the vascular smooth muscles. The activity of these muscles is under the control of the nervous system and they do not show spontaneous activity. This classification between muscles having a purely myogenic activity and the other group depending on nervous control was certainly useful, but now appears too rigid and outdated. Recent electro-physiological, neurohistochemical and electron microscopic investigations have shown that several

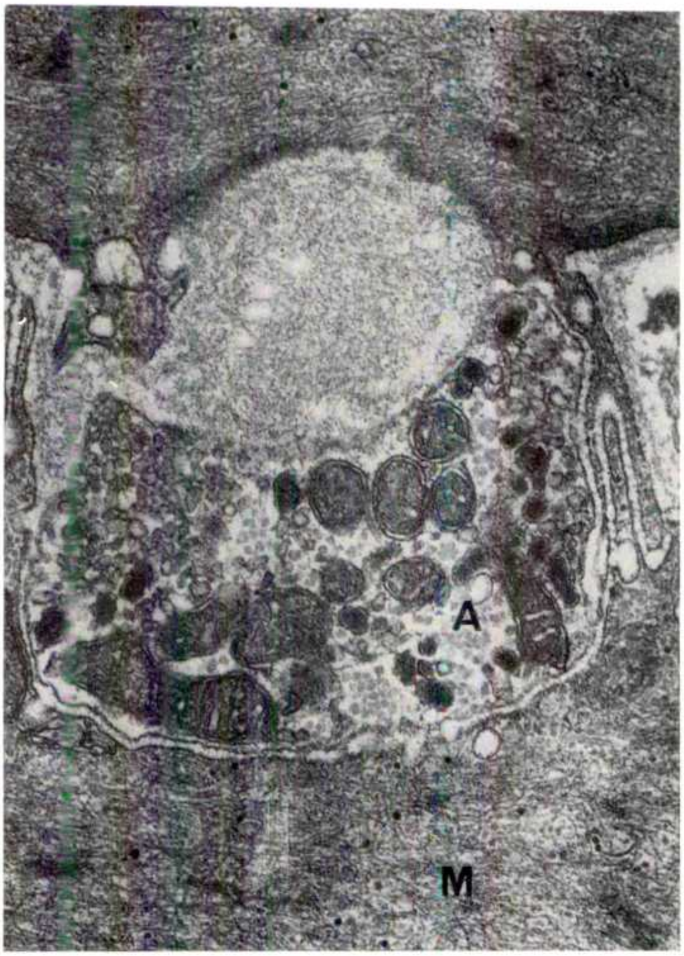


Fig. 7. Neuromuscular junction: close contact between a terminal axon (A) lying in a depression of a muscle cell (M). × 46,000.

smooth muscles, such as the bladder and the alimentary canal, show features pertaining to both groups (see review by Burnstock, 1970 and Bennett, 1972).

Therefore, a classification embodying these new data has recently been proposed by Burnstock (1970). It is essentially based upon the type of relationship existing between the peripheral autonomic nervous system and the smooth musculature.

Various ultrastructural studies have shown that the smooth muscle innervation can be quite different from one organ to another (Taxi, 1965; Burnstock, 1970).

The results of our investigations suggest a model of the autonomic innervation of the ureter according to the general pattern of innervation of the smooth musculature proposed by Burnstock *et al.* (1971) with the following main features (Fig. 11):

1. *Musculo-Muscular Connections*

The smooth muscle cells of the ureter are interlinked by specialised contact-areas. The closest connection is represented by the *nexus* characterised by a fusion-area between the external lamellae of the cellular membranes.

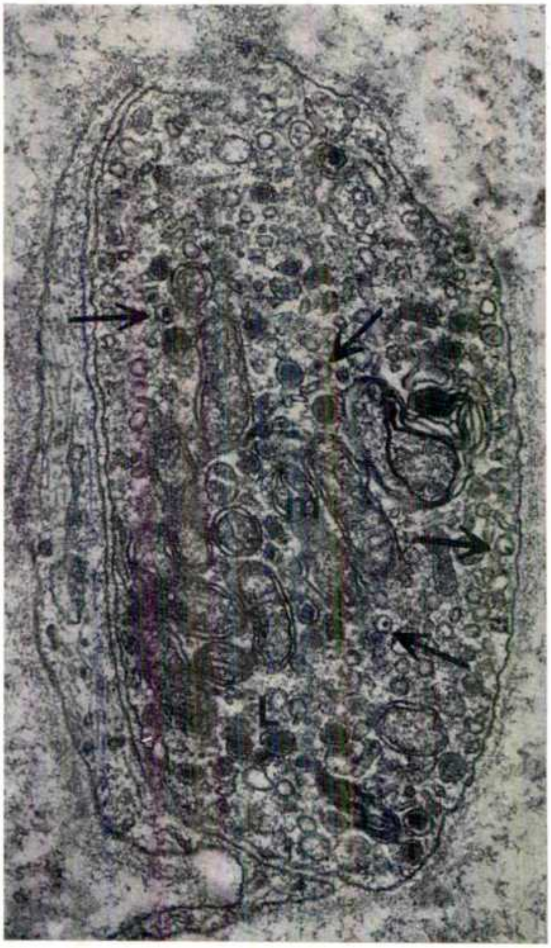


Fig. 8. Adrenergic nerve terminal: the axon contains small dense-cored vesicles storing noradrenaline (arrows) and also a few large granular vesicles (L) and mitochondria (m). ×48,000.

It is now generally accepted that these contact-areas constitute sites of lower electric resistance to the impulse transmission from one cell to another (Burnstock, 1970).

2. *Direct Innervation*

Rare ureteric muscle cells are directly innervated by terminal varicosities depressing the smooth muscle cell and separated by a narrow gap of 200 Å only.

3. *Coupled or Pluricellular Innervation*

The directly innervated cells are electrically coupled to the adjacent muscle cells by lower electric resistance areas represented by the nexuses.

4. *Indirect or Fasciculated Innervation*

The indirectly coupled cells, which are the most numerous in the ureter, are not directly activated by the transmission of the action potential of the contraction. The neurotransmitters (noradrenaline

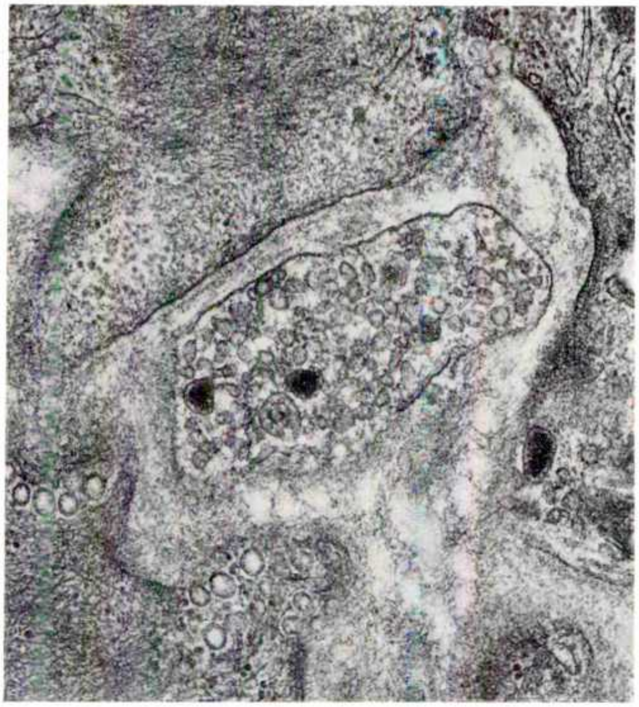


Fig. 9. Cholinergic nerve terminal in close relationship with smooth muscle cell. The axon is composed of small agranular (empty-looking) vesicles and a few large granular vesicles. ×49,000.

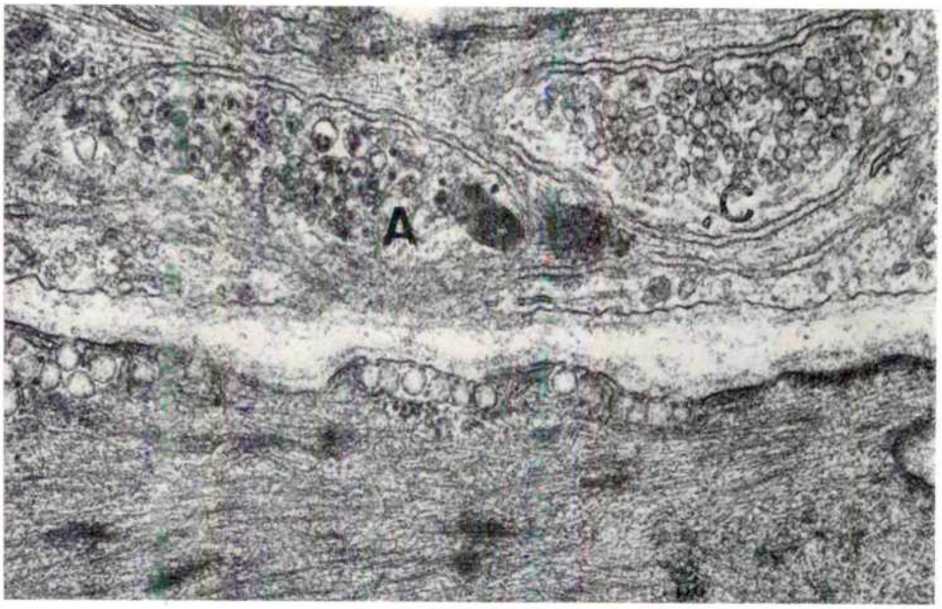


Fig. 10. Electron micrograph of human ureter treated with 5-hydroxydopamine. An adrenergic axon contains heavily granulated vesicles (A), whereas the cholinergic nerve (C) remains unaffected by this treatment and contains only empty-looking vesicles. The two kinds of nerve are observed running in close relationship in the same nerve fibre and this provides morphological evidence suggesting a possible interaction between adrenergic and cholinergic nerves. ×46,000.

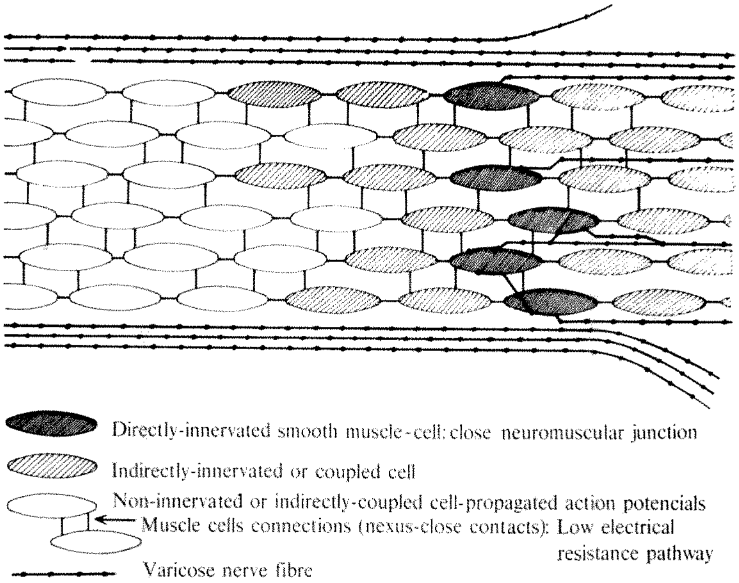

Directly-innervated smooth muscle-cell: close neuromuscular junction
Indirectly-innervated or coupled cell
Non-innervated or indirectly-coupled cell-propagated action potencials
Muscle cells connections (nexus-close contacts): Low electrical resistance pathway
Varicose nerve fibre

Fig. 11. Schematic representation of an ultrastructural model of the ureteric innervation (*modified from Burnstock* et al., 1971).

or acetylcholine) may be released by passing ("*en passage*") from the varicosities of the preterminal and terminal nerve fibres. These chemical mediators may influence smooth muscle cells at distances from 800 to 10,000 Å (Burnstock, 1970).

Thus, through one or more axonal varicosities, a single nerve fibre may influence several smooth muscle cells (Grillo, 1966).

Ureterovesical Ganglionic Structures

The existence of ganglia in the ureter is a controversial question. In a previous neurohistochemical investigation, we always noted the presence of ganglionic structures in the terminal portion of the ureter. The structures observed are part of a ureterovesical ganglionic complex located in the adventitia of the lower ureter, between Waldeyer's periureteric musculature and the juxta-vesical ureter, at the level of the ureteric orifices, in the posterior bladder musculature and trigone extending to the bladder neck (Schulman *et al.*, 1972, 1973).

The ureteric ganglia are made of typical neurons, the classical structure of which will not be further described in this paper (Fig. 12). We mainly wish to stress the somewhat unexpected presence of adrenergic (sympathetic) nervous elements in these pelvic ganglia, classically considered to be essentially parasympathetic structures.

We observed adrenergic nerve terminals characterised by small synaptic vesicles storing a typical dense-cored granule and located close to the ganglion cells sometimes making synapses with dendrites (Fig. 13).

Another type of adrenergic structure was also distinguished in the ureterovesical ganglia, namely small cells containing numerous large dense-cored vesicles having an approximate diameter of 2,000 Å (Fig. 14). These cells have a smaller size than the typical neurons and moreover differ from them by their large amounts of granular vesicles allowing comparison of these structures to the chromaffin cells of the adrenals (Elfvin, 1968). These cells show short processes coursing near the intra-ganglionic blood vessels. It is considered that these small granular cells can release a chemical neurotransmitter (noradrenaline or dopamine) which is able to influence

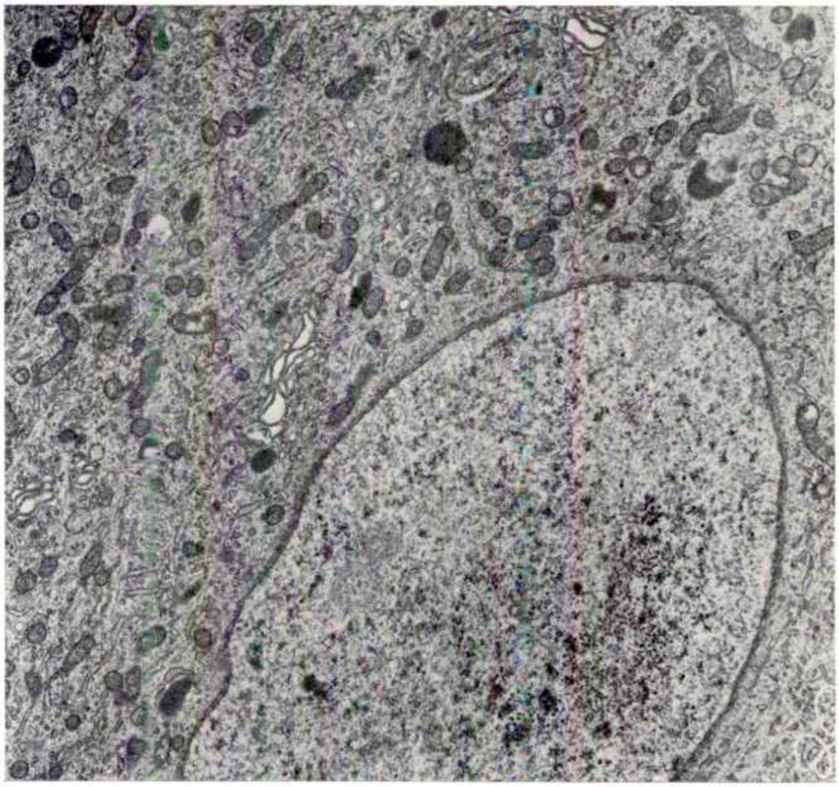


Fig. 12. A typical neurone from ganglia located in the adventitia of the terminal ureter. ×9,800.

at a distance a large number of receptors such as neurons, effector cells and capillaries (Siegrist *et al.*, 1968; Matthews and Raisman, 1969; Williams and Palay, 1969; Watanabe, 1971; Eränkö and Eränkö, 1971; Kanerva, 1972.)

Recent physiological and pharmacological studies have demonstrated the existence of adrenergic mechanism which can modulate the activity of sympathetic ganglia. The adrenergic structures are considered to have an inhibitory influence in the control of ganglionic activities (see review by Norberg and Sjoqvist, 1966).

Both types of adrenergic structures observed in the ureterovesical ganglia can play such a role.

These ganglionic structures can modulate the activity of the terminal ureter and the bladder and co-ordinate the influence of sympathetic and parasympathetic elements during micturition.

Summary

The fine structural aspects of the innervation of the human ureter were studied under the electron microscope.

Smooth muscle cells are interconnected to each other in areas of close contacts. The narrowest connection is represented by a *nexus*. This structure is of great importance in relation to the mechanism of transmission of impulses in intermuscle fibre conduction since it represents low resistance pathways between cells allowing transmission of the muscle contraction.

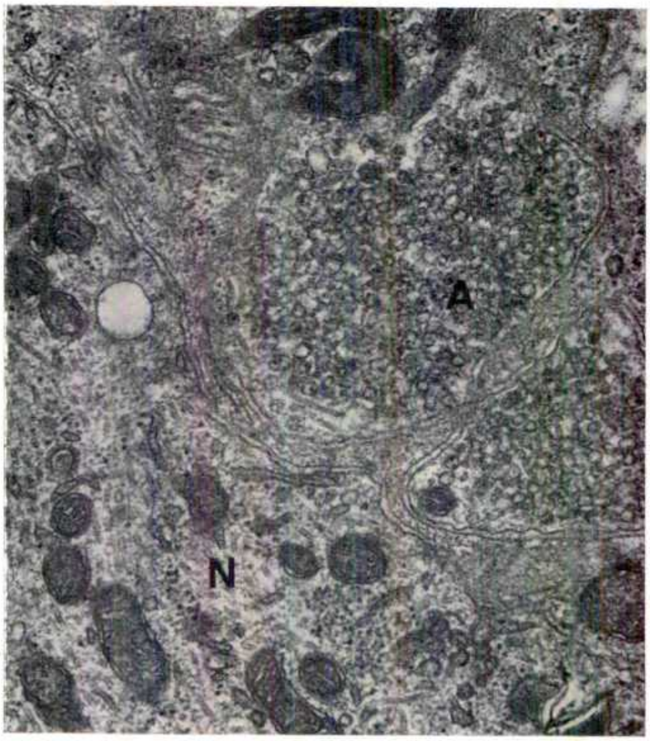


Fig. 13. Ureteric ganglia: adrenergic nerve endings (A) containing small granular vesicles in close relationship with a neurone (N). ×27,600.

The ureteric musculature receives both adrenergic sympathetic and cholinergic parasympathetic innervation. With the aid of 5-hydroxydopamine, a "false" sympathetic transmitter useful as a specific marker for adrenergic nerve endings, the two kinds of axon were observed in the same nerve bundle in close association with each other. This suggests a possible interaction between adrenergic and cholinergic nerves in the ureter. Cholinergic nerve endings may possibly act as sensory receptors.

Rare neuromuscular junctions were observed between nerve terminals and smooth muscle cells. However, nerve terminals do not innervate each muscle cell in a smooth muscle bundle but neurotransmitters liberated from "en passage" varicosities of the nerve fibres may influence several muscle cells at a distance. Ureteric peristalsis is essentially a myogenic phenomenon but ultramorphological evidence is provided for a regulation of this spontaneous activity by the autonomic nervous system and local reflex actions may also exist.

Ganglionic cells were found in the terminal portion of the ureter only. These typical neurons were part of an ureterovesical ganglionic complex. Adrenergic nerve elements were observed in these ganglia, namely: adrenergic nerve endings and catecholamine-containing cells. The significance of these results is discussed since these structures can modulate the ganglionic activity and integrate the function of the terminal ureter and the bladder during micturition.

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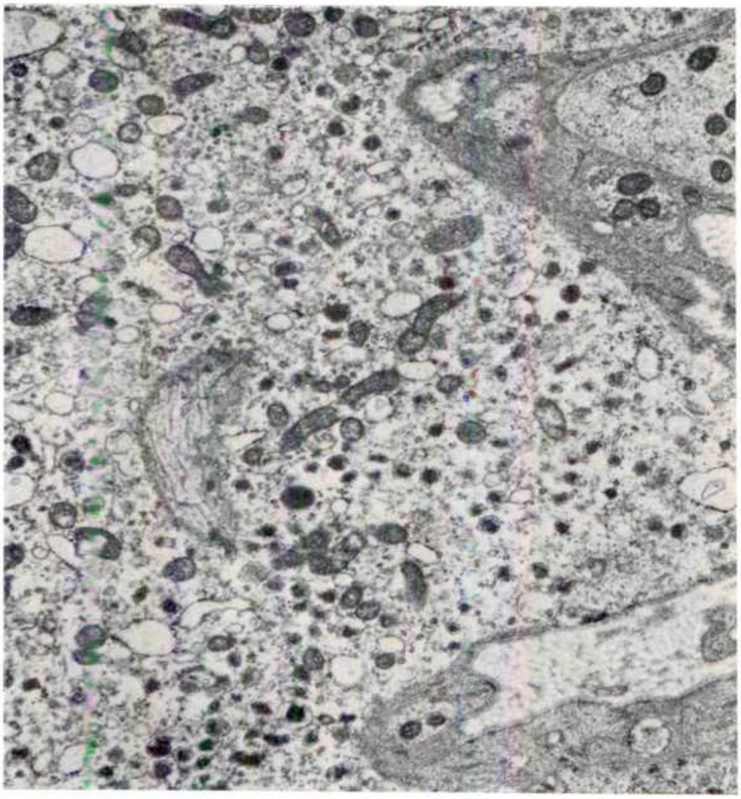

Fig. 14. Ureteric ganglia: granule-containing cell filled with large granular vesicles storing catecholamines. × 9,800.

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Vitamin B_{12} Absorption in Patients with Ileal Resection

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Booth and Mollin (1959) showed that the terminal ileum is the site of vitamin B_{12} absorption and there are many papers referring to the reduction of absorption after ileal surgery (Fone *et al.*, 1961; Fromm, Thomas and Hofmann, 1973). However, most of these series were composed of patients with various diseases and in whom widely differing lengths of bowel had been removed. There is no series in which short standardised lengths of bowel had been resected. Although Steyn (1972) has shown that the serum levels of vitamin B_{12} in patients with ileal conduits remain normal, McBrien (1973) showed that the absorptive power of ileum lying in the pelvis during radiotherapy for carcinoma of the bladder can be adversely affected. The purpose of this paper is to assess the absorption of vitamin B_{12} in patients in whom part of the terminal ileum has been excluded from the faecal stream in the course of urological surgery.

Materials and Method

36 patients were studied (Table I). 33 of these patients had an ileal conduit fashioned, 2 patients had an ileocystoplasty and 1 patient had a colonic conduit fashioned when the prepared ileal segment was rejected after a carcinoid tumour was found in it. A history of peptic ulcer and its surgical management was sought. Previous treatment with radiotherapy was noted. The serum vitamin B_{12} was estimated and a Schilling test was carried out. This test is used to measure the efficiency of the alimentary absorption of vitamin B_{12}. An oral dose of radio-labelled vitamin B_{12} is given and is closely followed by a large parenteral dose of non-radioactive vitamin B_{12} in order to saturate the plasma transport mechanism and liver stores and thus cause the absorbed radio-labelled vitamin B_{12} to overflow and be excreted in the urine.

Table I

Vitamin B_{12} Absorption
Patients Studied

Ileal Loop	33		
		29	Carcinoma of Bladder
		1	Ectopia Vesicae
		1	Myelomeningocele
		1	Carcinoma of Cervix
		1	Epispadias
Ileocystoplasty	2		Tuberculosis of Bladder
Colonic Loop	1		Ileal Loop Rejected—Carcinoid

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

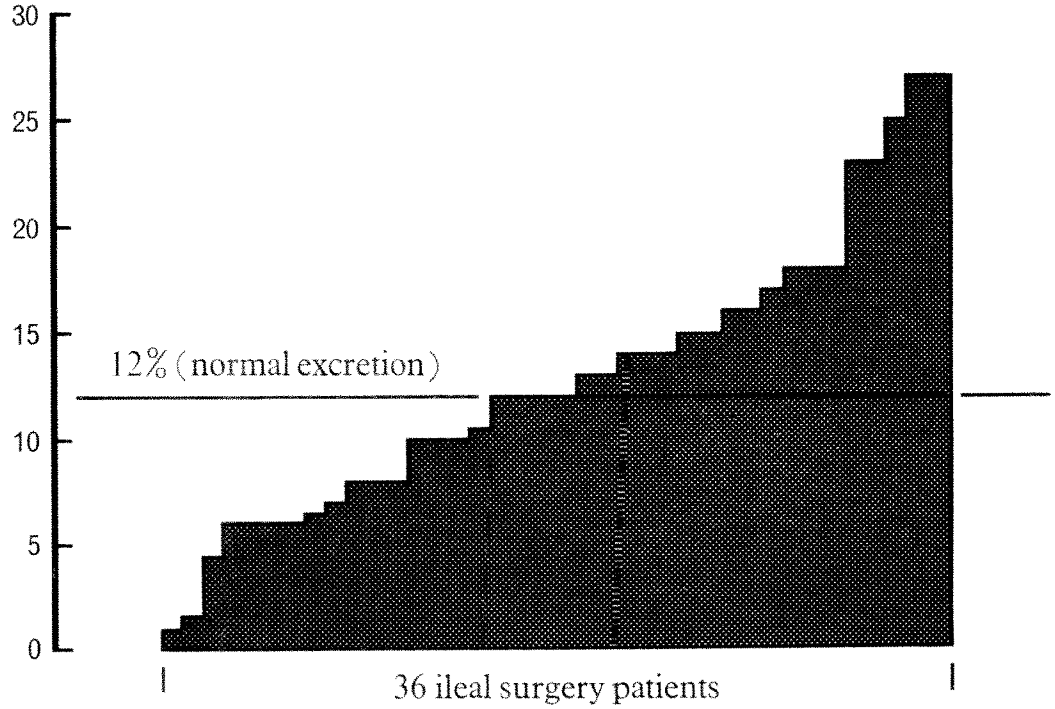

Fig. 1. Histogram of percentage excretion of ^{58}Co B_{12}.

1 microcurie of cobalt-58-labelled vitamin B_{12} was given orally to fasting patients followed half an hour later by 1,000 mg of non-radioactive vitamin B_{12} intramuscularly. All urine excreted in the 24 hours starting 2 hours after the oral dose of radio-labelled vitamin B_{12} was given was collected, and the fraction of the radioactive dose of cobalt excreted was estimated. An excretion of 12% or greater of the radioactive dose was accepted as normal absorption. In order to exclude those patients with gastric mediated malabsorption of vitamin B_{12}, the test was repeated with the addition of 1 USNF unit of hog intrinsic factor (Schilling, Clatanoff and Korst, 1955).

Results

The range of radioactive vitamin B_{12} excretion in this series is shown in Figure 1. Excretion of 12% or greater was achieved in 20 out of 36 patients, and in 16 patients there was defective excretion. Of the 16 patients with abnormal absorption without intrinsic factor, 1 developed metastases and was excluded from further follow-up. The remaining 15 patients had a further Schilling test with added intrinsic factor. 5 of these patients achieved normal absorption but 10 patients had persistently reduced absorption.

Discussion

Callender and Evans (1955) confirmed Schilling's observation of the same year, although with a larger series, that although the normal range of vitamin B_{12} absorption was wide, it was consistently above 12% (Fig 2). In the present series, 20 out of 35 patients had normal absorption. Of the remaining 15 patients, 5 had normal absorption after the exhibition of intrinsic factor,

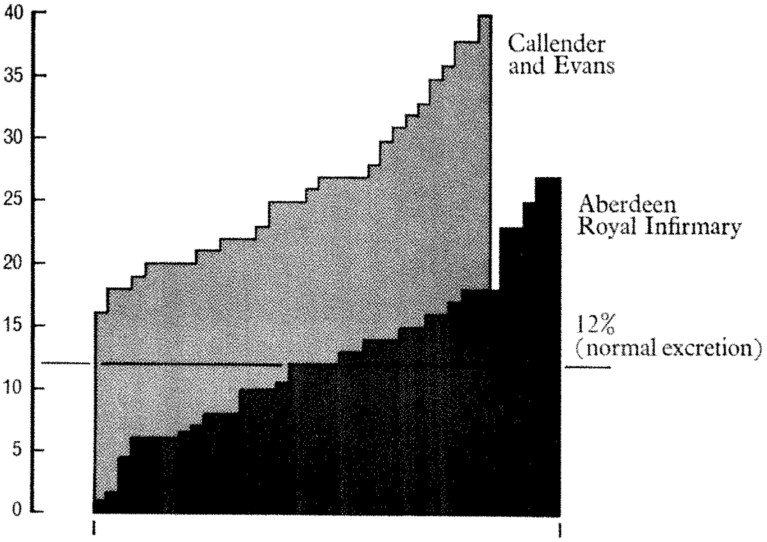

Fig. 2. Histogram comparing percentage excretions of ^{58}Co B_{12} of normal patients (after Callender and Evans) and patients in the present series.

Table II

Influence of peptic ulcer and surgical management on vitamin B_{12} absorption

		History of Peptic Ulceration	
		(Surgical intervention)	
Normal	20	1	1
Gastric Malabsorption	5	1	1
Ileal Malabsorption	10	2	1

demonstrating that they have gastric mediated vitamin B_{12} malabsorption. The other 10 patients had no response to intrinsic factor and thus the malabsorption must be related to a defect in the terminal ileum. In none of these patients was there a history of Crohn's disease or other cause of small bowel dysfunction.

There were 4 patients with a history of peptic ulceration of whom 3 required surgical treatment. These patients were evenly distributed in the 3 groups of patients (Table II) and therefore peptic ulceration and its surgical management is not an important factor in the malabsorption of vitamin B_{12} in this study.

McBrien (1973) showed that radiotherapy for carcinoma of the bladder can diminish vitamin B_{12} absorption and suggested that this had been caused by irradiation of terminal ileum lying in the pelvis close to the target organ. The distribution of patients treated preoperatively with radiotherapy is shown in Table III. Of the 35 patients in whom studies were completed, 14 had received previous radiotherapy. In those patients with normal ileal absorption of vitamin B_{12}, 8 out of 25 (32%) had received radiotherapy. But in those patients with ileal malabsorption, 6 out of 10 (60%) had been exposed to radiotherapy. Therefore there is an increased incidence

Table III

Influence of preoperative radiotherapy on ileal absorption of vitamin B_{12}

Vitamin B_{12} Absorption Effect of Radiotherapy				
		Radiotherapy		No radiotherapy
Normal	20	7	32%	13
Gastric Malabsorption	5	1		4
Ileal Malabsorption	10	6	60%	4
	35	14		21

of ileal malabsorption in those patients in whom ileal surgery was preceded by radiotherapy (Fig. 3). Nevertheless, although 6 out of 14 patients who had radiotherapy had ileal malabsorption, malabsorption also occurred in 4 out of 21 (19%) patients in whom surgery to the terminal ileum had not been preceded by radiotherapy.

The liver stores of vitamin B_{12} in normal well-nourished adults will last for between 2 and 5 years before depletion and only when this has occurred will the serum vitamin B_{12} level fall. But, although once that has happened, megaloblastic anaemia or subacute combined degeneration of the cord has been recorded as developing rapidly (Chanarin, 1969), serum vitamin B_{12} levels estimated at regular intervals could be regarded as adequate safeguard where facilities for investigations involving isotopes were not readily available.

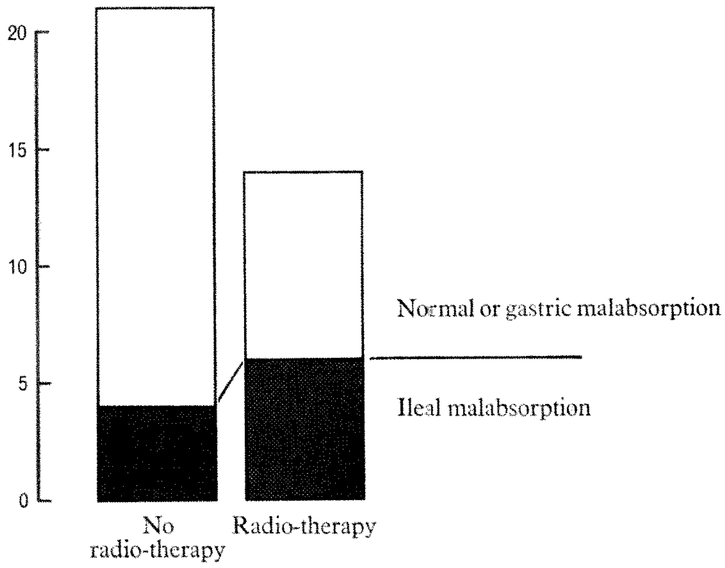

Fig. 3. Influence of preoperative radiotherapy on ileal absorption of vitamin B_{12}.

Conclusion

It is shown that many of the patients subjected to urinary diversion via ileal conduit or other procedure removing part of the terminal ileum from the faecal stream may as a result have malabsorption of vitamin B_{12}. The Schilling test has demonstrated those patients thus affected and in these patients maintenance vitamin B_{12} therapy is indicated.

Summary

Depression of vitamin B_{12} absorption in patients in whom part of the terminal ileum was removed from the faecal stream was investigated.

28% of the patients were shown by the modified Schilling test to have deficient ileal absorption of vitamin B_{12}.

These patients should be treated with vitamin B_{12} supplements.

We wish to thank Dr A. D. Dawson of the Department of Haematology and Dr R. Seymour and Mr I. Hendry of the Department of Medical Physics, University of Aberdeen, for their helpful advice and technical assistance in this study.

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An Appliance-free Ileocaecal Urinary Diversion: Preliminary Communication

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The long-term results of urinary diversion by ureterosigmoidostomy (Riches, 1967; Jacobs, 1967), ileal or colonic conduits (Schmidt *et al.*, 1973; Dretler, Hendren and Leadbetter, 1973; Mogg, 1967) and cutaneous ureterostomy (Rickham, 1964) are well documented. A critical analysis of the results shows a surprisingly high incidence of complications (Blandy, 1964), quite apart from their interference with the quality of life.

An alternative, appliance-free urinary diversion, must be sound in principle and technique, simple to manage, preferred by patients; and as emphasised by Bricker (1957), renal function should not be jeopardised by our attempts to provide continence.

A continent bowel ileostomy following total proctocolectomy is well established (Kock, 1969; Cameron, 1973) and this form of continent ileal pouch has also been used as a urinary reservoir (Kock, 1969; Tagart, 1974). Gilchrist *et al.* (1950) have described the use of the isolated ileocaecal segment as a substitute bladder, with continence dependent upon the antiperistaltic function of the terminal ileum, the action of the ileocaecal valve and the small ileal skin stoma (Merricks and Gilchrist, 1954; Sullivan, Gilchrist and Merricks, 1973). Other authors have found this ileocaecal reservoir to be incontinent (Harper *et al.*, 1954).

Having a personal preference for the use of caecum in construction of a cystoplasty, where metabolic absorption problems are rare, provided the upper renal tracts are normal (Worth and Turner-Warwick, awaiting publication) and experience of using the spouted ileum as a reflux preventing substitute for ureter when implanted into the bladder, a combination of these techniques has been developed to produce a continent uretero-ileocaecal reservoir which can be emptied by intermittent catheterisation via a skin flush ileostomy stoma.

Materials and Methods

Distension of isolated ileocaecal segments in the postmortem room, and barium enema studies in life, confirmed that the ileocaecal valve was incompetent in over 50% of cases, but that suturing a spout of ileum into the open end of the caecum or ascending colon produced a competent valve (Fig. 1).

X-ray studies under the image intensifier confirmed that the ileocaecal reservoir could be emptied by catheterisation of the spouted ileum (Fig. 2).

Technique

The bowel is prepared for 2 days with neomycin, magnesium sulphate and a verepaque enema (Plumley, 1966).

Using a long midline abdominal incision, the right colon and terminal ileum are mobilised. The colon is divided between the ileocolic and right colic arteries or between the divisions of the right colic artery. The ileum is divided about 15 cm proximal to the ileocaecal valve and the next 20 cm of ileum is also isolated on its blood supply later to form the ileal spout and skin flush ileostomy (Fig. 3).

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

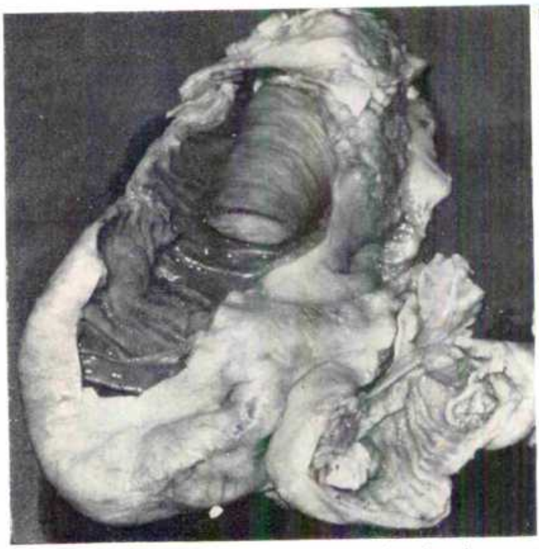


Fig. 1. Uretero-ileocaecal reservoir specimen showing the competent ileal spout hanging within the caecal reservoir. The distance from the surface ileostomy to the ileal spout is short to enable easy catheterisation of the caecal reservoir.

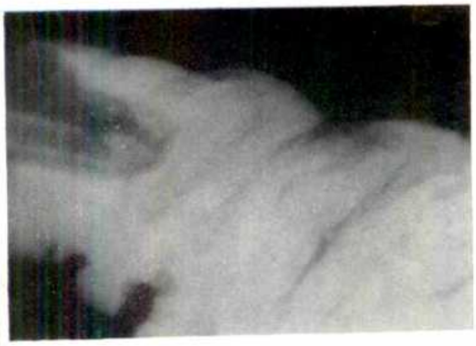


Fig. 2. Caecogram showing the competent ileal spout with the empty catheter about to enter the caecal reservoir for drainage.

The appendix is removed. The ureters are split, cuffed and intubated (Turner-Warwick and Ashken, 1967) and transplanted into the antemesenteric border of the terminal ileum, the end of the ileum then being closed and buried into the mesocolon (Fig. 3).

The ureteric spouts minimise the risk of reflux and pyelonephritis, and in some cases the uretero-ileal anastomoses will be protected from back pressure from the caecal reservoir by a competent ileocaecal valve.

The isolated ileum is then cuffed to form an isoperistaltic or preferably an antiperistaltic spout, at least 5 cm in length, which is sutured into the open end of the caecum or ascending colon (Fig. 4) and anchored to its anterior wall to try and prevent prolapse of the ileal spout as the pressure rises within the urine filled ileocaecal reservoir.

A full thickness disc of the anterior abdominal wall is excised in the right iliac fossa and the caecum around the ileal spout is anchored to the abdominal wall using 4 circumferentially placed linen sutures to buttress the ileocaecal reservoir and ensure a short and easy passage of a catheter into the urinary reservoir. The lateral space between the right colon and peritoneum is closed.

Bowel continuity is restored with an end-to-end ileocolic anastomosis. Continuous drainage of the ureters and caecum is maintained for 2 weeks, after which intermittent catheterisation is done about every 4 hours.

When indicated, a total cystourethrectomy or anterior pelvic evisceration is performed at the same operation, prior to construction of the urinary reservoir.

Preliminary Results

7 patients, 5 women and 2 men, between the ages of 36 to 72 years, have had an uretero-ileocaecal reservoir performed. In 4 cases, this was combined with a cystectomy or anterior pelvic evisceration for malignant disease. In 3 cases, a neurogenic bladder remained *in situ*, 2 requiring bladder washouts later for pyocystitis.

DIAGRAMS OF THE OPERATION. Fig. 3.A to E.

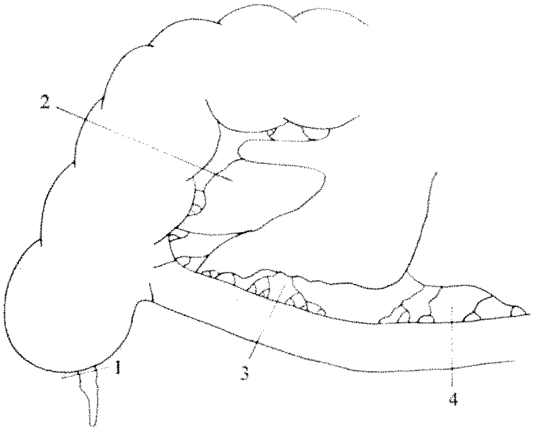


Fig. 3A. 1. Appendix removed. 2. Ascending colon divided below right colic artery. 3. Terminal ileum divided. 4. Length of ileum conduit isolated on its blood supply.

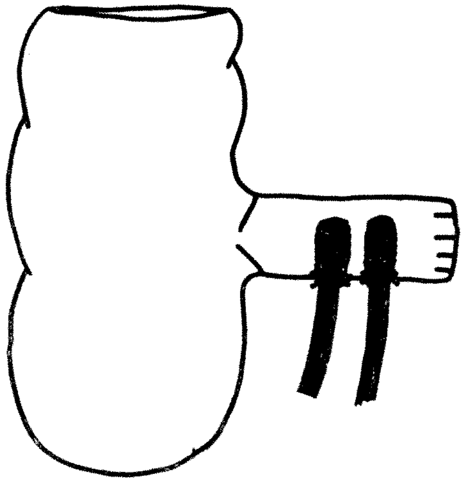


Fig. 3B. Ileum closed. Ureters split, cuffed and intubated with uretero-ileal anastomosis.

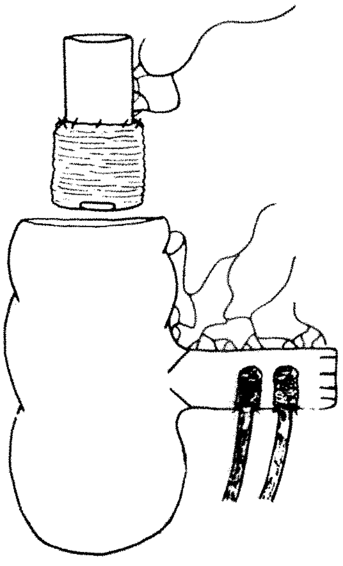


Fig. 3C. 5-6 cm. cuffed ileum.

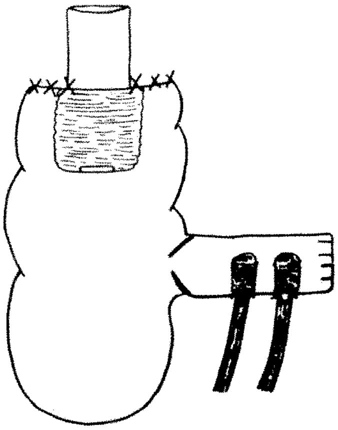


Fig. 3D. Ileal spout hangs within caecum for 5-6 cm. with closure of caecum around spout. This produces a competent valve.

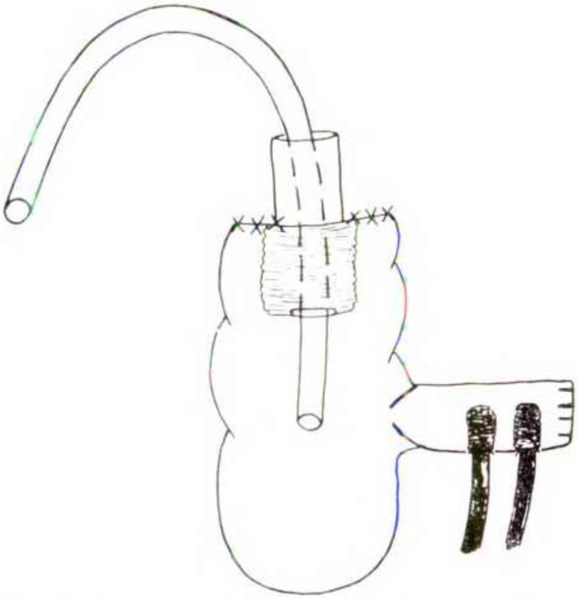
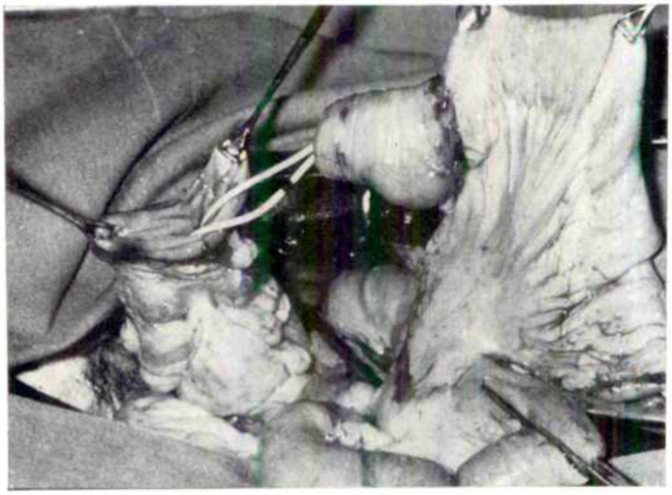


Fig. 3E. Urine syphoned off plus abdominal pressure to empty ileo-caecal reservoir by inserting the catheter into the skin ileostomy stoma through the competent spout into the caecum.



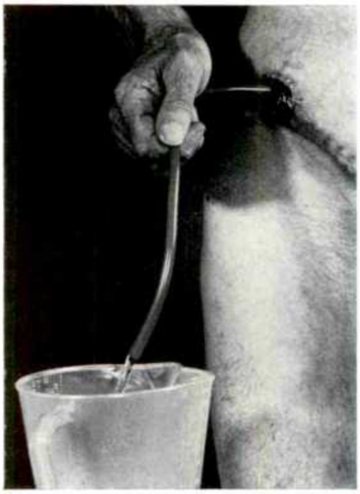


Fig. 4. At operation, the ileal spout is about to be sutured within the open end of the caecum. The spout must be anchored within the caecum to avoid later prolapse. Some of the redundant isolated ileum will be excised when the skin flush ileostomy stoma has been sited.

Fig. 5. Self-catheterisation of the ileostomy and caecal reservoir with drainage of clear urine.

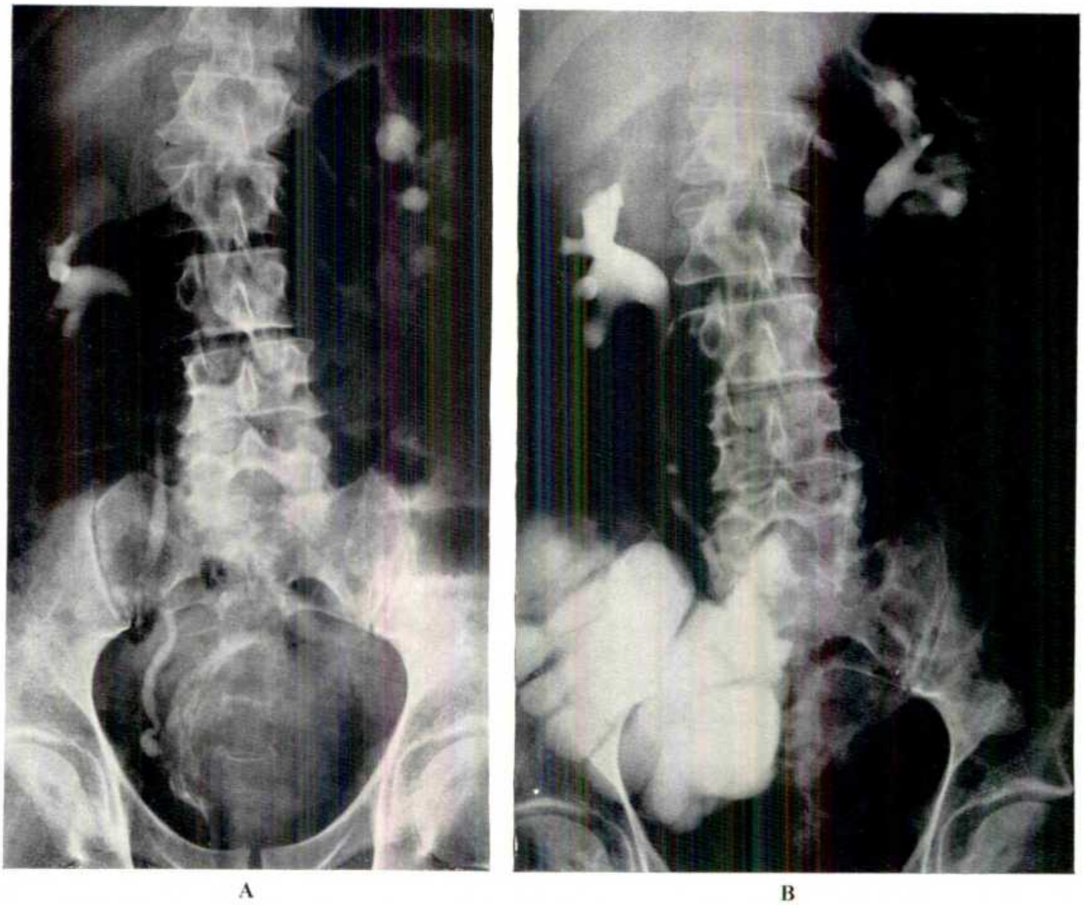


Fig. 6.A, Intravenous pyelogram with a large carcinoma of the bladder producing a left hydronephrosis.

Fig. 6.B, Intravenous pyelogram 3 months postoperatively with good concentration and drainage from both kidneys, resolution of the left hydronephrosis and filling of the competent ileocaecal reservoir.

For between 5 and 12 weeks postoperatively, 5 cases have managed self-catheterisation of their urinary reservoir about every 3 to 4 hours, with drainage of between 200-300 ml of urine containing diminishing amounts of mucus (Fig. 5). One patient has elected for continuous catheter drainage of the urinary reservoir at night. The catheters have been stored in Hibitane solution which has remained sterile and is changed twice a week. A feeling of distension occurs within the caecum as it fills and caecometrograms on 2 cases have shown a rise in pressure from about 20 cm of water with 300 ml of fluid in the reservoir to 70 cm of water with 350 ml in the caecum.

3 cases, who had been managing well at home, have developed *prolapse of the ileal spout* with some incontinence and difficulty of catheterisation, 7 to 12 weeks postoperatively. Peristalsis has been active in the prolapsed spouts, which have been easily reduced and reanchored within the caecum using non-absorbable sutures, with a return to urinary continence and self-catheterisation in 2 cases, but intermittent incontinence in the third case which is being managed with continuous catheter drainage.

At exploration the ileal spouts have looked healthy, without ischaemic or traumatic fibrosis. Peristaltic activity of the spouts probably contributes to their prolapse and antiperistaltic ileal spouts are now being fashioned.

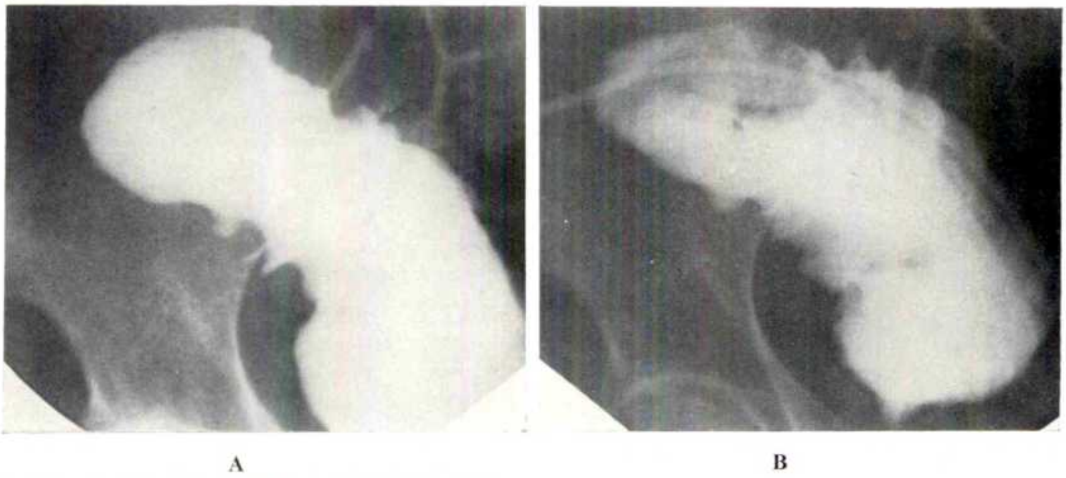


Fig. 7.A, Caecogram with no leakage from the reservoir.
Fig. 7.B, The ileal spout is visualised and the caecal reservoir is emptied by catheter drainage via the ileostomy.

2 patients developed extraperitoneal urinary *caecal fistulae* around the ileostomy and were treated with continuous catheter drainage of the reservoir. One of these patients died 5 weeks postoperatively, with a chest infection and renal papillary necrosis, secondary to severe diabetes mellitus complicated by an autonomic neuropathy and hypotension. The ileal spout had remained continent and healthy (Fig. 1).

One ileostomy behaved as an incontinent ileal conduit, probably due to caecal spasm and too short an ileal spout, and has been managed with an ileostomy appliance.

Intravenous pyelograms done in 3 cases, 2 to 3 months postoperatively have shown prompt concentration and drainage of the contrast from the kidneys with improvement of any previous hydronephrosis (Fig. 6, A and B).

Caecograms have demonstrated the competence and survival of the ileal spout (Fig. 7, A and B).

Metabolic absorption problems have not occurred during this short follow-up period, with normal blood ureas and creatinines and no hyperchloraemic acidosis. An early hypokalaemia was recorded in 3 cases and required potassium supplements. Vitamin B12 serum levels have been noted for comparison with later figures.

Clinical episodes of urinary tract infection with pyelonephritis have only occurred in the diabetic patient, although *pseudomonas pyocyaneus* have been cultured intermittently from the reservoir urine in 3 cases. Mandelamine and Vitamin C have been prescribed.

Interpretation and Significance of Results

It is too early to evaluate the potential use of this ileocaecal urinary reservoir in cases requiring urinary diversion.

It is hoped that using an antiperistaltic ileal spout, anchored with non-absorbable sutures within the caecal reservoir, will avoid the late complication of prolapse of the ileal spout.

The hypokalaemia noted may occur with any uretero-intestinal anastomoses (Williams *et al.*, 1967), but hyperchloraemic acidosis, recurrent pyelonephritis and stricture formation at the uretero-ileal anastomoses should continue to be less than after ureterosigmoidostomy or uretero-ileosigmoidostomy (Pinck, 1969; Moors *et al.*, 1973), and an appliance-free life seems preferable to the established methods of urinary skin diversion.

Should urinary continence not be achieved, the alternatives of a self-retaining catheter drainage or an ileostomy appliance still remain.

Summary

Whilst the early results were encouraging, the subsequent occurrence of prolapse of the everted ileal spout through the skin flush ileostomy remains a problem. This complication converts the previously continent ileocaecal reservoir into an incontinent conduit.

Modifications in the technique and construction of the ileal spout valve are being evaluated to prevent this prolapse which is due to a combination of peristalsis and rising pressure within the ileocaecal reservoir.

I wish to thank Mr N. Alan Green and Mr A. E. Kulatilake for their advice in developing this technique, Dr James Visick for the X-rays and Mr R. Burn for the photographs.

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The Control of the Uninhibited Bladder by Selective Sacral Neurectomy

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The so-called uninhibited, involuntary, irritable, spastic, hyperactive, unstable, over-facilitated, hypertonic, neurogenic bladder remains an enigma. In our current series of 304 incontinent patients uninhibited bladder contractions caused or potentiated the incontinence in 146 cases (48%). Only 12% of these had any neurological disease.

Drug treatment is unsatisfactory in the more severe cases. Enterocystoplasty and diversion to an ileal conduit carry a certain morbidity and may not be socially acceptable. As uninhibited contractions can be abolished by caudal anaesthesia or ganglionic blockade the hyperactivity must be mediated by nerves. Denervation of the bladder may provide an alternative therapy. We have chosen to assess the value of selective sacral neurectomy in the management of this condition.

Munro (1945) noted an improvement in bladder function following extensive anterior rhizotomy for spasticity. Several authors have since reported deliberate complete bladder denervation to allow autonomous activity (Misak *et al.*, 1962; Nagib, Leal and Voris, 1966). Total denervation also produces a paralysed sphincter and impotence. To avoid this the technique of pelvic neurotomy was developed by Thiermann (1953), and local denervation by perivesical dissection (cystolysis) has been advocated by Turner-Warwick (Worth and Turner-Warwick, 1973). It is difficult to judge the extent of denervation carried out during these procedures.

Heimburger, Freeman and Wilde (1948) developed the technique of selective sacral root blocks with local anaesthetic to define the bladder innervation. Meirowsky, Scheibert and Rose (1952) carried out these tests prior to selective sacral neurectomy, and a small number of patients have since been treated by this method (Susset *et al.*, 1969; Rockswold, Bradley and Chou, 1973). The results of operation, however, remain unpredictable. We have therefore performed a physiological assessment of the effects of sacral root blocks and selective sacral root section on bladder and sphincter function.

Patients and Methods

17 patients underwent bilateral selective nerve blocks of the roots S2-S4 in turn. A spinal needle was inserted under radiographic control through the posterior sacral foramina, and 1·5 ml of Marcain was injected to block the root as it passed through the anterior sacral foramen. After nerve blocks 9 of the patients were selected for sacral neurectomy.

These patients all suffered from urge incontinence and enuresis and all but 2 were leading a normal active life. None of the idiopathic cases exhibited any neurological signs. Before and after the nerve blocks and operation the patients underwent a routine urodynamic assessment. This assessment consisted of:

1. A cystometrogram with constant recording of bladder and intra-abdominal pressure during filling with saline at 37°C, at a constant rate of 50 ml per minute.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

2. Pressure/flow analysis during micturition.
3. Recording of urethral sphincter pressure, at rest and during voluntary contraction, by the urethral pressure profile technique (Brown and Wickham, 1969).

All parameters were electronically transduced and recorded on a polygraph. This urodynamic analysis was repeated 90 minutes after the nerve block and 3 months after the neurectomy.

Table

Case	Sex	Age	Aetiology	History	Complications
F.J./001	M	36	Multiple Sclerosis	5 years	Constipation
I.S./020	F	42	Idiopathic	4 years	? Prediabetic
M.B./019	M	21	Idiopathic	Lifelong	—
S.C./007	F	20	Idiopathic	Lifelong	Epilepsy
K.G./064	M	26	Idiopathic	Lifelong	—
M.S./075	M	21	Idiopathic	Lifelong	—
M.F./079	F	53	Cerebral vascular accident	4 years	Poor ambulation
P.M./090	F	25	Idiopathic	Lifelong	Epilepsy
B.G./158	F	32	Multiple Sclerosis	4 years	Poor ambulation

Operative Technique

The roots selected by sacral nerve block were exposed by a limited sacral laminectomy approach. This avoids intradural manipulation and does not interfere with the function of the lumbosacral junction. Under a light general anaesthetic, with spontaneous respiration, a mid-line incision is made between S1 and S4. After retraction of the muscles the relevant posterior sacral foramina are identified by counting up from S4 with reference to the sacral hiatus and to radiographs. A burr hole is then made in the lamina immediately cranial and medial to the selected foramen which exposes the nerve just below its exit. We have found that we can avoid damage to the posterior primary ramus by this method. Under the operating microscope the sacral root can be dissected into its constituent bundles. These are stimulated with a specially constructed bipolar electrode using a square wave stimuli at up to 5 volts at 10 cycles/second. The bladder pressure response is monitored through a fine urethral catheter, the urethral pressure is assessed by the profile technique and a balloon is placed in the anal sphincter.

Results

Selective Sacral Nerve Blocks

Assessment of the change caused by selective sacral nerve blocks shows that bladder capacity is significantly increased ($P<0{\cdot}005$) by injections at all 3 levels. The S.3 nerve root appears to be most concerned with bladder innervation and blocks at this level are most effective in increasing capacity and reducing uninhibited activity. In all but 1 case the bladder was still able to contract adequately and expel its contents, though the urinary flow rate is significantly reduced. On the contrary the only significant change in urethral sphincter activity is an increase in resting sphincter pressure after S4 block ($P<0{\cdot}05$). This suggests an inhibitory nerve supply to the urethral smooth muscle. Though the voluntary sphincter contraction was reduced in some cases no significant trend was observed on group analysis. These results suggested that sphincter paresis should not prove to be a complication of neurectomy and encouraged us to proceed to operation in certain cases.

Intra-operative Nerve Root Stimulation

At operation the exposed nerves were stimulated to confirm the sacral block findings and assess the relative contribution of the dissected nerve bundles to bladder and sphincter innervation. The bladder response to the stimulation of an undissected single nerve root is a sustained tonic contraction with a latency of 5-8 seconds. The urethral sphincter response is an immediate but poorly sustained contraction followed by a sustained relaxation. This relaxation may be further evidence that inhibitory fibres are contained in the sacral outflow to the sphincters. Differential stimulation of nerve root bundles after dissection showed that the rootlets are functionally distinct before their entry into the sacral plexus. Some are somatic and others para-sympathetic. In general it would appear that the lateral fibre bundles convey fibres destined for the bladder while the medially placed bundles appear to innervate the sphincters.

Selective sacral neurectomy

The level for neurectomy was selected by combining the information obtained by preoperative nerve root blocks and intra-operative nerve stimulation. The S3 roots were selected in 8 of the 9 cases. The 1 case in whom S4 was cut showed no postoperative improvement. All the female patients had bilateral nerve operations. The initial male patients had unilateral operations because of the fear of impotence. However as no such complication was observed subsequent bilateral operation was performed in 1 man with no diminution of potency. After bilateral nerve operation an indwelling catheter was required for periods up to a week. The patients suffered little postoperative discomfort and could be ambulant as soon as they recovered from the anaesthetic. 2 cases recorded symptoms of paraesthesiae in the buttock which persisted for up to 6 weeks after operation. Any numbness in the saddle area did not last for more than 2 or 3 days.

We have attempted to assess the response to selective sacral neurectomy as objectively as possible. The cystometrogram capacity was increased in 6 of the 9 patients postoperatively. The mean change was from 176 ml (±S.D. 112) to 315 ml (±S.D. 135, $P<0{\cdot}01$). This represents an increase of 70%. The capacity failed to increase in the 2 women with epilepsy and in 1 other case with considerable detrusor hypertrophy and indistensibility due to the longstanding hyperactivity. A normal desire to void occurs but the onset of this is delayed from 102 ml (±S.D. 68) to 215 ml (±132, $P<0{\cdot}05$).

The average volume voided is considered to be an index of functional bladder capacity. This is assessed by calculating the total urinary output over the period of a week and dividing this by the urinary frequency. This was increased in 4 cases but failed to increase in the other 3 who all carried a residual urine. 2 of these cases had multiple sclerosis (M.S.). The overall mean increase was from 140 ml (±S.D. 52) to 176 ml (±S.D. 76, P not significant). However, the maximum volume voided was significantly increased from 300 ml (±S.D. 100) to 396 ml (±S.D. 161, $P<0{\cdot}02$).

The index of uninhibited bladder activity used is the summated height of all uninhibited contractions divided by cystometrogram capacity, and expressed as mm Hg/ml. Uninhibited activity was reduced postoperatively in 8 of the 9 cases. The overall mean change was from 1·25 mm Hg/ml (±S.D. 1·00) to 0·47 mm Hg/ml (±S.D. 0·55, $P<0{\cdot}05$). There would thus appear to be a generally significant improvement in bladder function. The tone of the resting urethral sphincter, which is substantially involuntary, was insignificantly increased after operation from 62·3 mm Hg (±S.D. 24·7) to 68·5 mm Hg (±S.D. 32·8, P not significant). However the pressure produced by voluntary sphincter contraction was reduced slightly in 8 of the 9 cases. This significant alteration was from 109·5 mm Hg (±S.D. 54·3) to 84·2 mm Hg (±S.D. 37·4, $P<0{\cdot}05$).

It is important to stress that the patients were able to pass urine normally after this operation. The urinary flow rate was increased in the majority of cases postoperatively. The mean change was from 23·1 ml/sec (±S.D. 11·1) to 26·8 ml/sec (±S.D. 13·0, P not significant). However the mean volume voided at the test also increased from 175 ml to 321 ml. As it is known that the flow rate is proportional to the volume voided operation has made no effective difference to urinary flow rates. The intravesical micturition pressure shows no trend towards change, and the measurement of intra-abdominal pressure shows that patients do not have to strain post-operatively in order to void. Only 1 patient developed a residual urine where this had not been present preoperatively. In those cases with M.S. who had a preoperative residual, this was not increased when considered as a percentage of capacity.

Objective assessment of symptoms showed that enuresis was cured in 2 cases, substantially improved in 4 cases and unchanged in 3. In the group that was improved the change in mean frequency of enuresis was from 5·5 to 1·5 times a week. The cases that failed were the 2 young females with epilepsy and 1 case of severe reflex incontinence with totally inadequate sensation. This case continually extruded her catheter preoperatively but now is adequately controlled by this method. Urinary frequency shows a trend towards improvement though this is not significant. The overall change is from 10·5 x/day (±S.D. 5·47) to 7·5 x/day (±S.D. 2·2, P not significant). Urge incontinence was cured in 6 of the 9 cases, being unchanged in the 3 cases whose enuresis failed to respond.

There was no deterioration of sexual potency among the 4 men operated upon. One case of M.S. who had been impotent for 5 years had potency transiently restored. Another patient reported a marked increase in the frequency of sexual activity. No significant disturbance of bowel function has been recorded and in particular no constipation. One case of M.S. has obtained some spontaneous bowel action after 3 years of manual evacuation.

Discussion

The aim of this technique is to increase functional bladder capacity by reducing uninhibited activity without compounding the problem of incontinence by interfering with sphincter function. The results as presented above show that 2 patients have been cured, 5 improved and 2 remain unchanged. This initial response to surgery is very encouraging as far as bladder function is concerned. No patient has been made worse by the procedure but there are 2 conspicuous problems. Firstly, the procedure failed to improve 2 cases, and secondly, sphincter function has been shown to be depressed though in no case has this been clinically significant.

Both the failures were young females suffering from epilepsy. In one case an S4 nerve section was performed on the basis of sacral block results, which were not confirmed by stimulation at operation. It is our conclusion that intra-operative stimulation is a more accurate means of localising the innervation of the bladder than are sacral nerve blocks with anaesthetic. We feel that intra-operative stimulation and recording is mandatory. Preoperative investigation by selective sacral nerve blocks is probably unnecessary except in cases of grossly asymmetrical partial upper motor neurone lesions. In these cases sacral blocks are the only way to identify preoperatively the final common pathway of asymmetrically mediated neural hyperactivity.

The other failure had 3 nerve roots ablated but urge incontinence and enuresis persisted. This patient had a thick walled bladder that could not be distended under any form of anaesthesia to more than 315 ml. In retrospect it is evident that if the capacity after anaesthesia is less than 400 ml neurectomy should not be performed and hydrostatic balloon distension or enterocystoplasty should be recommended. It is therefore essential that some test of maximum potential bladder capacity should be used in all cases.

Although the analysis of sphincter pressure shows that the voluntary activity of the urethral sphincter is reduced after neurectomy, this has not affected the threshold of continence because the effect on the sphincter remains less profound than that on the bladder. Nevertheless, it is important that less destructive surgical techniques should be sought. The results of sacral rootlet stimulation have independently confirmed the observation made by Harman (1899) that the somatic and parasympathetic fibres are topographically distinct at nerve root level. Microscopic dissection should allow the isolation of detrusor innervation, and a selective rootlet neurectomy may then be performed. Section of the whole nerve root may still be indicated in cases that combine an uninhibited bladder with a spastic or dysco-ordinated sphincter.

Assessment of the results suggests that the best clinical response follows bilateral neurectomy at 1 level. A single nerve section is inadequate in these more severely incontinent patients. Triple nerve section may provoke a residual urine. The level for most operations would appear to be S3, but this must always be confirmed by stimulation. The combination of adult enuresis and diurnal urge incontinence is particularly difficult to treat, because of the possible dysfunction of higher neural centres.

The follow-up at present lies between 6 and 18 months, and it is therefore too early to be optimistic about long-term results. However no case has yet shown any regression after the first postoperative month. The initial results are sufficiently encouraging for this form of treatment to be continued. The technique obviously requires refinement and continuous reassessment, but seems a relatively atraumatic procedure, at any rate for the patient. We would offer the following criteria for the selection of incontinent patients for sacral neurectomy.

1. The case should be of urge incontinence, reflex incontinence or enuresis where conservative treatment has failed.
2. Urodynamic assessment should confirm that incontinence is due to uninhibited activity, exclude sphincter weakness and outflow tract obstruction, and show that sensation from the bladder and urethra is relatively intact.
3. A potential functional capacity in excess of 400 ml must be demonstrated by caudal block, sacral root block or general anaesthetic.

In incomplete upper motor neurone lesions with an asymmetrical or focal neurological deficit, selective sacral nerve blocks should be performed to elucidate focal abnormalities of bladder innervation. In all cases intra-operative nerve stimulation should confirm the root level supplying the majority of bladder fibres. Rootlet stimulation at this level should allow the isolation of bladder and sphincter innervation. The neurectomy usually should be bilateral at 1 root level. Where there is bladder hyperactivity with a normal sphincter, selective section of parasympathetic rootlets only is indicated. Where bladder and sphincter spasm are combined total root section can be carried out.

Summary

The effects of denervation in patients with severe diurnal and nocturnal incontinence due to uninhibited bladder contractions has been objectively assessed.

A reversible prediction of the effects of bladder denervation by performing selective sacral root blocks has shown that S3 root block produces the greatest depression of uninhibited activity and increase of bladder capacity, without significant interference with sphincter function or detrusor paresis. Subsequent sacral neurectomy in 9 patients produced 2 cures, 5 cases improved and 2 unchanged.

Diurnal urge incontinence responded better than enuresis. There was a significant overall improvement in cystometrogram capacity and uninhibited activity, but the voluntary sphincter pressure was impaired slightly.

Comments on the selection of cases for denervation are made.

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Prolonged Bladder Distension as a Treatment of Urgency and Urge Incontinence of Urine

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Urgency of micturition, which at its worst results in urge incontinence, is a common urological syndrome and may vary in severity from a social nuisance to a serious incapacity. In the absence of a specific treatable cause, such as infection or urethral obstruction with retention, the underlying lesion is obscure, although recent work (Bates *et al.*, 1970) suggests that detrusor hyperactivity is present in many, if not all, of these cases.

Drug treatment with propantheline or imipramine is adequate in mild cases but fails in the more severe cases. Occasionally the symptoms are sufficiently severe to warrant treatment by surgery either by operation on the bladder, such as cystocystoplasty (Turner-Warwick and Ashken, 1967; Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973), enterocystoplasty (Gibbon, 1967), multiple detrusor myotomy (Mahony and Laferte, 1972) or by division of the parasympathetic nerves (Thiermann, 1953; Marshall, 1954; Gibbon, 1967). All these procedures involve major surgery, are not uniformly successful, and some may have side-effects such as the development of impotence in the male.

Distension of the bladder is a procedure used in this condition often unwittingly and may well account for the beneficial effects of cystoscopy. However, the duration and pressure of the dilatation has been haphazard and we can find no reports of pre- and postoperative bladder pressure studies using this technique.

The use by Helmstein (1966) of prolonged hydrostatic pressure in the treatment of carcinoma of the bladder and our own research into the basic physiology of distension (Dunn, 1974) suggested that it might have a place in the management of this common and distressing condition. We describe here the early results in a group of 20 patients treated by prolonged bladder distension under epidural anaesthesia.

Patients

Each patient in this series gave a history of urge incontinence with the exception of 2 who had severe urgency and frequency of urine without incontinence. A full urological examination was carried out to exclude any urinary tract abnormality and urinary infection. Neurological abnormalities were excluded by clinical examination.

The patients were then selected by the following criteria:

(*a*) they had failed to obtain any reasonable symptomatic improvement from either medical or surgical treatment;
(*b*) they were so inconvenienced by their symptoms that they were willing to undergo an experimental procedure and
(*c*) cinecystourethrography and cystometry demonstrated an uninhibited or unstable bladder.

Procedure

Pressure flow cystourethrography as described by Moolgaoker *et al.* (1972) and cystometry was performed preoperatively and these studies were repeated again postoperatively. Cystometry

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was carried out with the patient supine. The patient was asked to hold the urine whilst the bladder was filled with saline at a constant rate of 100 ml per minute until uncomfortably full. The patient was asked to cough and strain and was then tilted into the upright position and asked to cough and strain again. Bladder capacity was estimated with the patient horizontal and the patient then voided sitting (female) or standing (male).

Prolonged distension of the bladder was carried out after high epidural anaesthetic with the exception of 1 patient who was given a general anaesthetic because of previous surgery on the lumbo-sacral spine.

Each patient was cystoscoped and the bladder capacity measured. An 18F Foley catheter with a condom securely tied just proximal to the balloon was introduced into the bladder. The technique of distending the bladder hydrostatically was similar to that described by Helmstein (1972). The bladder was distended to a pressure equal to the patient's systolic blood pressure for 4 30-minute periods. At the end of each period the bladder was emptied and the capacity measured. The catheter was then removed and the following day the patient was allowed home.

Results

The striking feature at cystoscopy was the presence of trabeculation varying from mild to moderate in every patient despite the absence of evidence of outflow obstruction. The bladder capacity at the start of the procedure and at the end of each 30-minute distension was recorded. In all patients the bladder capacity increased with successive periods of distension (Fig. 1).

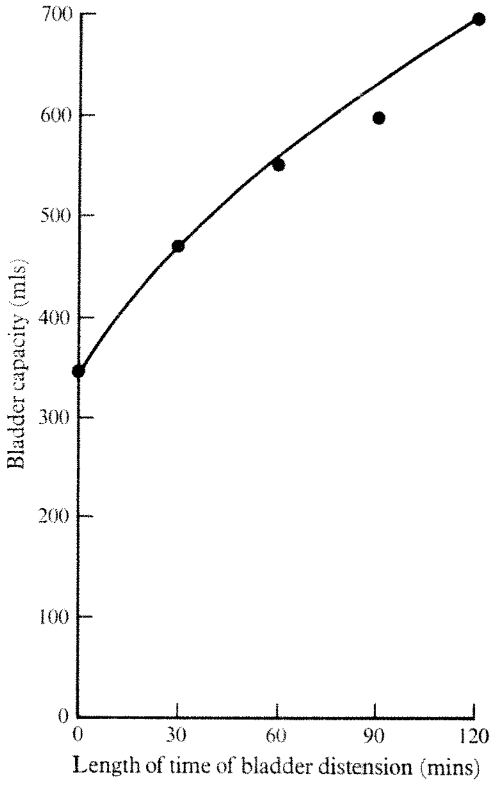


Fig. 1. A typical example of the change in bladder capacity during prolonged bladder distension.

Table I

Principal Symptoms of Patients with Urgency and Urge Incontinence

Patient	Age	Sex	Day symptoms		Night symptoms		Patients' comment on results	Length of follow-up
			Pre-op	Post-op	Pre-op	Post-op		
WG	29	F	F 10-20 mins U+++ I+	F 2-3 hourly U− I−	Wet every night	None	Excellent	10/12
†JB	17	F	F 15 mins U++++ I+	F 3-4 hourly U− I−	Wet every night	Wet every night	Improved	9/12
MH	65	M	F+20-30 mins U++++ I+	F 2-3 hours U+ I−	F 1 hourly Wet every night	F 2 hourly dry	Excellent	8/12
*BL	61	F	F 20-30 mins U++++ I+	F 2-3 hourly U+++ I−	F 2 hourly Occasionally wet	F 4 hourly dry	Improved	6/12
ST	62	F	F 1-2 hourly U++++ I+	F 3-4 hourly U− I−	F 3 hourly dry	None	Excellent	6/12
PA	19	M	F 15 mins U+++ I−	F 4-5 hours U− I−	None	None	Excellent	6/12
MS	39	F	F 15 mins U++++ I+	F 2-3 hourly U++ I+	F 2 hourly dry	F 4 hourly dry	Improved	6/12
SH	57	M	F 5-10 mins U++++ I+	F 2 hourly U− I−	F 30-45 mins Wet every night	F 2 hourly dry	Excellent	6/12
†VS	29	F	F 30 mins U++++ I+	F 1 hourly U++++ I+	Wet every night	Wet every night	Not improved	6/12
MM	19	F	F 20-30 mins U+++ I+	F 3 hourly U− I−	F 3 hourly dry	None	Excellent	6/12
PT	37	F	F 1 hourly U++++ I+	F 3 hourly U− I−	Wet every night	None	Excellent	5/12
CJ	39	F	F 2 hours U++++ I+	F 3-4 hourly U− I−	F 3 hourly Wet occasionally	None	Excellent	4/12
TF	24	F	F 10-15 mins U++++ I+	F 2-3 hourly U− I−	Wet every night	None	Excellent	5/12
VK	56	F	F 1 hourly U++++ I+	F 3 hourly U− I−	Wet every night	None	Excellent	5/12
MC	56	F	F 1 hourly U++++ I+	F 2-3 hourly U++ I−	1 hourly dry	3 hourly dry	Improved	4/12
DK	17	M	F 1 hourly U++++ I+	F 3 hourly U− I−	Wet every night	Wet 1/2 nights per week	Improved	4/12
DD	38	F	F 1 hourly U++++ I+	F 3 hourly U− I−	F 2 hourly dry	None	Excellent	3/12
OCJ	68	F	F 20 mins U++++ I−	F 3-4 hourly U− I−	F 1 hourly dry	None	Excellent	3/12
PB	21	M	F 20 mins U+++ I+	F 2-3 hourly U− I−	Wet every night	None	Excellent	3/12
JS	66	F	F 2-3 hourly U+++ I+	F 4 hourly U− I−	Wet occasionally	None	Excellent	3/12

F = frequency of urine (approximate average).
U = urgency (intensity as described by patients).
I = incontinence.
* Patient had general anaesthetic.
† These patients have had second distension.

The symptoms of each patient before and after prolonged bladder distension are summarised in Table I. 14 patients were completely cured of their symptoms, 5 showed some improvement in frequency, urgency and incontinence, 2 of these patients becoming dry and the remaining patient showed no improvement following prolonged bladder distension.

Cinecystourethrography and cystometric studies were carried out on all patients preoperatively and again 2-3 weeks postoperatively. Preoperatively 18 patients demonstrated spontaneous detrusor contractions on filling, with leakage of urine (Fig. 2). The remaining 2 patients showed spontaneous and induced detrusor contractions on coughing, straining or elevation (Fig. 3) with no urinary leakage. In all patients the bladder capacity was small varying from 50 ml to 350 ml, with a mean value of 241 ml.

The 14 patients, who claimed complete symptomatic relief, at postoperative cystometric assessment all showed considerable increase in bladder capacity. The cystometrograms were normal (Fig. 4) with the exception of 2 patients who still demonstrated spontaneous detrusor contractions on filling and 1 patient who leaked urine. The 5 patients who had improvement in symptoms all showed increase in bladder capacity, 2 had a normal cystometrogram but in

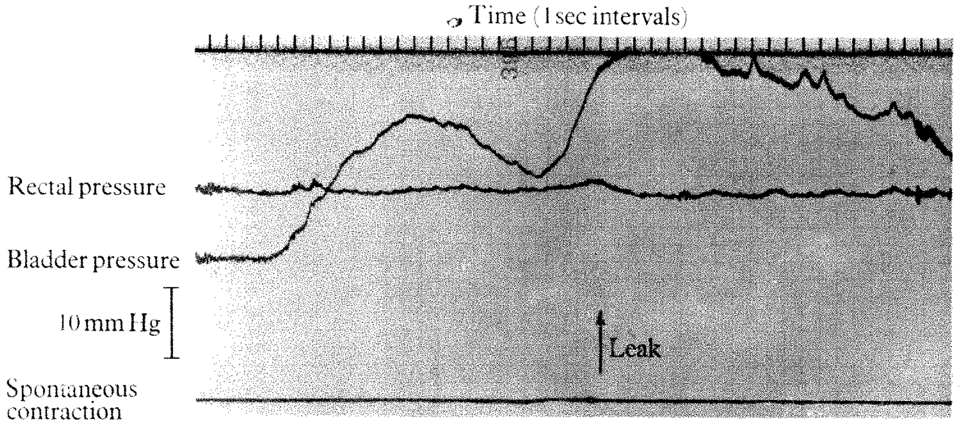


Fig. 2. Cystometrogram showing a spontaneous bladder contraction.

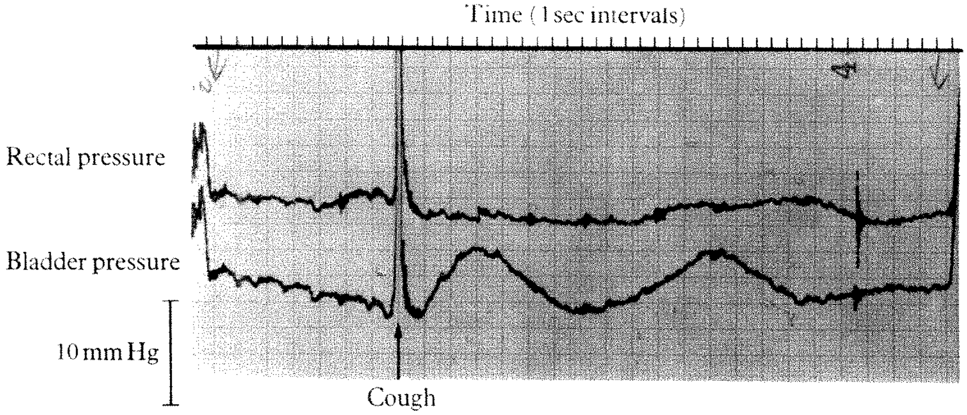
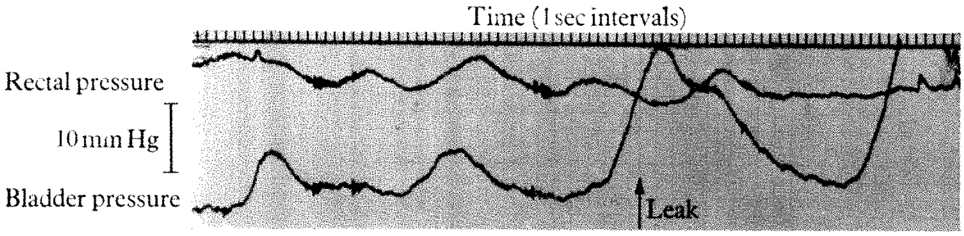


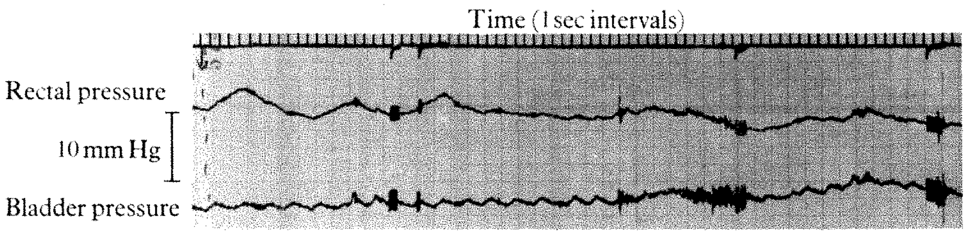
Fig. 3. Cystometrogram showing a cough-induced bladder contraction.

the remaining 3 either spontaneous or induced detrusor contractions were still demonstrated. The only patient who showed no symptomatic improvement showed no real change on cystometry except for some increase in bladder capacity (Table II).

Further follow-up studies have been carried out on all patients 3 months postoperatively and 11 at 6 months. These have shown that the initial improvement is maintained.



Pre-op cystometrogram. At capacity



Post-op cystometrogram. At capacity

Fig. 4. Comparison of pre- and postoperative cystometrograms in a patient who became symptom-free following prolonged bladder distension.

Discussion

The mechanism by which prolonged bladder distension is effective is unknown. It could be the result of ischaemia of the mucosa, nervous tissue, or muscle of the bladder wall or physical damage of one of these by stretching during prolonged bladder distension.

The pressure and duration was chosen on the result of blood flow and pH studies (Dunn, 1974). Only further experience will show if this should be modified. The increasing capacity at each successive distension suggests that a single short period of distension may well be inadequate in these severe cases.

Hodgkinson (1965) drew attention to the normal ability to inhibit bladder contractions. Preoperatively all the patients in this series were unable to inhibit bladder contractions but following prolonged bladder distension over half the patients were able to inhibit bladder contractions during cystometry. Although very prolonged distension may result in atony of the bladder (Mayo *et al.*, 1973), in our series no patient had any difficulty in initiating micturition and all were able to void to completion.

Bladder instability could be due to a sensory abnormality in the bladder wall and since the mucosa and submucosa are subjected to the maximal effect of bladder distension it is possible that ischaemic or mechanical damage to the submucosal afferent nerve plexuses or stretch receptors might be responsible for the loss of bladder irritability.

Table II

Pre- and Postoperative Cystometric Findings and Bladder Capacities During Bladder Distension

	Pre-op cystometry		Features at operation			Post-op cystometry	
Patient	Capacity	Comments	Cystoscopic appearance	Bladder at start	Capacity at finish	Capacity	Comments
WG	250 ml	Spontaneous and induced contractions	Mild trabeculation	300 ml	600 ml	450 ml	Normal cystometrogram
†JB	190 ml	Spontaneous and induced contractions	Mild trabeculation	350 ml	640 ml	390 ml	Normal cystometrogram
MH	160 ml	Spontaneous and induced contractions	Moderate trabeculation	450 ml	790 ml	390 ml	Normal cystometrogram
*BL	120 ml	Spontaneous and induced contractions	Mild trabeculation	400 ml	750 ml	300 ml	Spontaneous contractions
ST	180 ml	Spontaneous and induced contractions	Mild trabeculation	700 ml	1200 ml	650 ml	Normal cystometrogram
PA	320 ml	Spontaneous contractions No leakage	Mild trabeculation	480 ml	720 ml	500 ml	Normal cystometrogram
MS	300 ml	Spontaneous and induced contractions	Mild trabeculation	500 ml	765 ml	560 ml	Spontaneous and induced contractions with leakage
SH	350 ml	Spontaneous and induced contractions	Mild trabeculation	550 ml	1050 ml	400 ml	Normal cystometrogram
†VS	Less than 50 ml	Spontaneous contractions	Mild trabeculation	280 ml	570 ml	100 ml	Spontaneous and induced contractions with leakage
MM	140 ml	Spontaneous and induced contractions	Mild trabeculation	300 ml	450 ml	300 ml	Spontaneous contractions with leakage on one occasion
PT	280 ml	Spontaneous and induced contractions	Moderate trabeculation	400 ml	630 ml	490 ml	Normal cystometrogram
CJ	340 ml	Spontaneous contractions No leakage	Mild trabeculation	600 ml	1150 ml	480 ml	Normal cystometrogram
TF	300 ml	Spontaneous and induced contractions	Moderate trabeculation	700 ml	1000 ml	460 ml	Normal cystometrogram
VK	110 ml	Spontaneous contractions	Moderate trabeculation	250 ml	700 ml	310 ml	Normal cystometrogram
MC	350 ml	Spontaneous contractions	Mild trabeculation	550 ml	1150 ml	600 ml	Spontaneous contractions
DK	350 ml	Spontaneous contractions	Moderate trabeculation	350 ml	675 ml	520 ml	Normal cystometrogram
DD	330 ml	Spontaneous and induced contractions	Moderate trabeculation	650 ml	1200 ml	550 ml	Normal cystometrogram
OCJ	240 ml	Spontaneous and induced contractions	Mild trabeculation	450 ml	900 ml	410 ml	Spontaneous contractions No leakage
PB	220 ml	Spontaneous and induced contractions	Mild trabeculation	490 ml	750 ml	400 ml	Normal cystometrogram
JS	50 ml	Spontaneous contractions	Moderate trabeculation	350 ml	675 ml	310 ml	Normal cystometrogram

* Patient had a general anaesthetic.

† These patients have had a second distension.

Conclusions

Prolonged distension of the bladder may be a useful technique in the management of patients with urgency and urge incontinence of urine. It is a relatively simple procedure if epidural anaesthesia is available. Patients need only be in hospital for 2 days. Complications are few. In 1 patient the condom ruptured during distension and following removal of the catheter a part of it remained in the bladder but was easily retrieved at further cystoscopy and 1 patient had backache, at the site of the epidural, for 3 weeks postoperatively.

Summary

20 patients with urgency and urge incontinence were treated by prolonged bladder distension.

14 patients were completely cured of their symptoms. 5 showed improvement whilst in 1 patient symptoms remained unchanged.

These early results seem good enough to warrant the further use of prolonged distension of the bladder for the treatment of urgency and urge incontinence.

We are extremely grateful to Miss Penelope Fursdon and Miss Wendy Hills for their excellent technical assistance with the cystourethrography and cystometry. We would like to thank the Anaesthetic staff of the United Oxford Hospitals, in particular Dr Bryce-Smith, for the skill and the time spent in providing epidural anaesthesia. Finally we are indebted to Mrs Jean Broadis for her patience and kindness in the preparation of the manuscript.

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Clinical Application of Electronic Bladder Stimulation in Paraplegics

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In the last 2 decades great progress has been made in the care of patients with neurogenic bladders. The development of antibacterial therapy for urinary tract infections, the recommendation of intermittent catheterisation in place of continual catheter drainage, and the judicial use of operative procedures to relieve obstruction or to divert the urine, have all reduced the urologic morbidity and mortality associated with this problem. There are still some patients, however, who continue to have recurrent urinary tract infections, who do not develop a satisfactory reflex bladder, and who do not respond satisfactorily to intermittent catheterisation.

The initial report of stimulation of the spinal cord and pelvic nerves occurred over 100 years ago (Budge, 1864). In the intervening years a stimulus has been given to the pudendal, hypogastric and pelvic nerves as well as the bladder, in animal laboratories. Clinical experimentation was initiated by Dees in 1940 using an intrarectal probe, and intravesical catheter-electrodes (Katona, 1958) and electrodes implanted into the detrusor muscle have also been used. The failure rate in these early studies was high and prompted our interest in a more satisfactory means of achieving complete micturition.

Materials

Our initial laboratory efforts (Friedman, Nashold and Senechal, 1972) involved acute and chronic experiments on cats and dogs. Surface stimulation of the lumbar and sacral spinal cord elicited excellent bladder pressures, but without micturition. Highest bladder pressures were obtained at the S2 level. Stimulation above S1 induced activation of skeletal muscle with contraction of the perineal musculature and tonic-clonic movement in the lower extremities.

Use of a depth electrode induced similar bladder pressures with voiding. Descending visceral motor pathways for the bladder lie in the medial portion of the lateral columns and it was felt that positioning the electrodes within the central grey matter induced their activation. Subsequent autopsy examination of adult human spinal cords yielded an average depth for the intermediolateral grey column in the sacral cord of 2·5 mm. The chronic depth electrodes now used consist of 2 platinum-iridium wires 2·5 mm in length and 2·5 mm apart, mounted on a Silastic clip.

The electric parameters found most helpful include a biphasic square wave at 15-20 cycles per second. The stimulus is applied for 20-30 seconds using 10-15 volts.

Clinical experimentation using this stimulator was begun in 1970 and has been used in 10 patients (Nashold *et al.*, 1972; Grimes, Nashold and Currie, 1973). The procedure was approved by the medical committee on human experimentation and the experimental nature was discussed with the patient and his family.

Procedures

Careful patient selection and evaluation should be conducted before consideration of implantation of a spinal cord stimulator. In this initial patient group, only paraplegics have been con-

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sidered, to avoid the possible complication that sensation of pain would preclude adequate stimulus. Patients who might be treated by intermittent catheterisation or external sphincterotomy should be excluded. Those patients with persistent vesicoureteral reflux or with trabeculated fixed bladders are also excluded. Traumatic cord lesions must not involve the conus medullaris or the cauda equina. A lapse of 1 year from time of trauma to consideration of stimulation should be enforced in order to evaluate any return of function.

Patient evaluation includes a complete history and physical examination, including neurologic examination. Urinalysis, urine cultures, and renal function studies including blood urea nitrogen, creatinine, and creatinine clearance are performed. Cystourethrography and panendoscopy are used to evaluate the lower urinary tract and bladder capacity and voiding pressures are measured. Urethral pressure profiles are helpful in evaluating the external urethral sphincter. Intravenous urography helps to evaluate the upper urinary tract while myelography may be obtained to demonstrate the level of the cord lesion.

With the patient under general anaesthesia, a T12 to L1 laminectomy is done exposing the cauda equina and the conus medullaris. Serial measurements of bladder pressure are then obtained by stimulating the cord surface with a special bipolar electrode. At the level producing the highest bladder pressure, the depth electrode is positioned and held in place by dacron mesh strips. Electrode lead wires are tunnelled subcutaneously to the anterior abdominal wall and there connected to a radiofrequency receiver.

Intermittent or continuous catheter drainage is maintained for 1 week postoperatively before bladder stimulations are begun. As the patient becomes familiarised with the technique of stimulation, it is employed every 4 hours for emptying the bladder and the catheter is removed.

Results

Our series now includes 6 male and 4 female paraplegics who have undergone implantation of a spinal cord bladder stimulator. The longest is 45 months postoperative and the most recent is 1 month. The age range is 14-40 with an average of 21·8 years. The average interval from time of accident to implantation of the stimulator is 26 months and the longest has been 4½ years. An automobile accident was the aetiologic factor in 7 patients' paraplegia, falls accounted for 2 and a gunshot wound of the thoracic spinal cord for 1. No patient had urinary tract disease prior to his accident, but all had worn an indwelling catheter for at least a portion of their management since the accident, and 1 patient had undergone a cystolithotomy.

The patients are maintained in the hospital until they are able to void satisfactorily using the stimulator. They are then followed on a regular basis in the out-patient clinics. A urinalysis and determination of residual urine are performed at every visit and urine culture and sensitivities are obtained when necessary. A micturition cystogram is obtained every 6 months and intravenous urography is obtained yearly.

3 males and 3 females now rely completely upon the bladder stimulator for purposes of micturition. 2 of the males required external sphincterotomies after implantation of the stimulator while none of the females required further surgical therapy. All of these patients remain totally continent of urine and maintain average residual of zero to 10 ml. Their incidence of infection is markedly reduced.

One patient died 7 months after implantation of the stimulator due to pneumonia and hepatitis. In that interval he had voided satisfactorily and required no surgery of the vesical neck or external sphincter. He had had one urinary infection and his residual urine was 20 ml.

2 patients have been unable to void satisfactorily with the stimulator and are failures. The first suffered a T7 fracture dislocation in an automobile accident. His sacral cord was smaller than normal and the electrode was positioned at the S1 level. Poor bladder pressures were obtained and despite resection of the bladder neck and external sphincter he was unable to void. The stimulator was moved to a lower position on the cord and excellent bladder pressures

Table I

Summary of Patient Experience

Patient	Age	Sex	Level of injury	Bladder	Capacity	Postop rx	Pressure cm H20	Follow up	
								u/a	res. u.
S.A.	15	M	T11	spastic	100	B.N.	80-90	inf.	0
C.W.	19	M	C6	atonic	550		80-90	inf.	20
T.B.	25	F	T8	atonic	130		80-90	inf.	5
B.P.	14	M	T7	atonic	650	B.N. sph.	70-80	Foley	
S.W.	22	M	T6	atonic	400		80-90	0	30
T.B.	17	M	C2	atonic	560	sph.	70-80	0	2
T.L.	20	M	T3	atonic	600	B.N. sph.	70-80	Foley	
J.B.	29	F	T12	irritative	250		80-90	0	40
M.J.	17	F	T4	spastic	350		80-90	0	5
D.S.	40	F	T4	spastic	150		70-80	0	40

obtained, but he was never able to void satisfactorily. The second patient received a stimulator 35 months after a T3 fracture dislocation. Excellent bladder pressures were obtained but he was unable to empty the bladder satisfactorily, in spite of resection of the vesical neck and external sphincter. He dislikes intermittent catheterisation and is maintained on an indwelling catheter.

One patient received the stimulator 1 month ago and is currently still adapting to its use. She partially empties the bladder but has required occasional intermittent catheterisation.

Discussion

Our experience demonstrates some of the difficulties involved in treating the paraplegic patient. The type of bladder response the patient will ultimately develop cannot be predicted by anatomic level of bony fracture or by sensory levels. 2 patients in this series had cervical spine fracture-dislocations but flaccid bladders. Many patients have mixed lesions and are not easily classified as an upper motor neuron or a lower motor neuron lesion.

The initial animal investigations support the concept of a physiological micturition centre localised in the sacral cord. Tower's studies (1937) indicate that neurons below the level of cord trauma remain intact both anatomically and physiologically. Implantation of a stimulator into the spinal cord was evolved to take advantage of this intact micturition reflex system.

Localisation of the stimulus to the intermediolateral grey columns involves parasympathetic motor activity. Other autonomic responses indicate that excess stimulus is produced. During active stimulation there is piloerection, and increased skin temperature below the level of the stimulus. Adductor spasm may be marked and occasional penile erection occurs, indicating multiple actions beyond simple detrusor contraction. Autonomic hyperreflexia has been seen in 2 patients in this series. This was probably related to the high level of the cord lesion in both, and was manifested by headache, hypertension, and bradycardia. These patients were treated with guanethidine until the hyperreflexia was controlled. Medication was stopped and the symptomatology has not recurred.

Technically the stimulator is very easy to use. The receiver unit is implanted in the anterior abdominal wall where it is easy to reach. The transmitting unit fits over this and the patient is able to control the cycles per second, the voltage, and of course the duration of the stimulus.

The ability of several patients to achieve both detrusor contraction and external sphincter relaxation simultaneously indicates that there may be a specific micturition centre located in the sacral cord. The fact that some patients have required external sphincterotomy after implantation reveals the difficulty encountered in placing the stimulator in this precise location.

Two general patterns of response have evolved. In one, sphincter relaxation accompanies detrusor contraction during stimulation and the patient voids to completion. In the second, the sphincter and bladder neck contract initially, but open completely when the stimulus is halted and the patient then voids. In this second pattern it is necessary to stimulate 2 or 3 times for 20-30 seconds before the bladder is completely emptied. Each pattern is specific for that individual patient and there is no changing from one to the other. Each female shows normal opening of the vesical neck and funnelling of the urethra at the initiation of the stimulus.

We have employed biphasic square-wave pulses in an effort to minimise adverse electrical effects on the spinal cord tissue, but some chronic scarring, of course is inevitable. To date there have been no changes in the electric parameters used which would indicate a histologic change around the stimulating electrode. Autopsy examination of the cord in our one death revealed minimal scarring at the site of implantation.

Average vesical pressures achieved with the stimulator have been 60-70 mm Hg. No patient has developed vesicoureteral reflux postoperatively nor has any undergone changes of the upper urinary tract. The frequency of urinary infections has been greatly reduced and when uninfected most patients maintain residual urines of less than 10 cc. All patients continue to have normal and stable renal function studies.

The complications seen with earlier direct bladder electrodes of breakage or migration of wires have not been encountered. There have been no wound infections or neurosurgical complications due to the operation. One patient developed a residual urine and urinary infection after the transmitting antenna became damaged, but cleared promptly when given a new antenna.

Conclusions

Our studies confirm evidence of a micturition centre located in the sacral cord. When the reflex arc is intact stimulation of the centre leads to satisfactory micturition. Precise localisation of the electrode is paramount in achieving satisfactory micturition. The regained ability to control one's urinary elimination without external or internal collection devices has reduced these patients' morbidity and improved their outlook on life.

Summary

A new bladder stimulator is presented in an effort to reduce urological complications of neurogenic bladders. Preoperative evaluation and operative techniques are discussed.

7 of 10 patients voided with the stimulator, maintain low residual urines, and a reduced infection rate. 2 patients were failures and 1 is still adjusting to the device.

Physiological mechanisms are discussed. Additional investigation of more precise localisation of stimulus is needed.

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The Vascular Contribution to Intraurethral Pressure

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The role that the sympathetic nervous system plays in the physiology of normal micturition has been debated for many years. Some believe that the internal urethral "sphincter" is under direct sympathetic control (Learmonth, 1931; Krane and Olsson, 1973) whereas others believe (Lapides *et al.*, 1958) that the sympathetic nervous system plays no part in micturition. An attractive proposal was put forward by Tanagho *et al.* (1969) that the effects noted with sympathetic stimulation acted only indirectly on the intramural urethral pressure by constricting the blood vessels in the urethral wall. This hypothesis is based on the belief that angiotensin is a pure vasoconstrictor. Angiotensin, however, acts on all smooth muscle, including urethral smooth muscle (Goodman and Gilman, 1970).

The following experiments were designed to show that the urethral pressure rise with angiotensin is separate from the blood pressure rise, insofar as the urethral pressure rise follows a different time sequence from the blood pressure rise after the intravenous administration of angiotensin. Furthermore, it will be shown that the effects of angiotensin on the urethra can be modified by α blockade, but the blockade has no effect on the blood pressure rise after angiotensin.

Materials and Methods

6 adult female mongrel dogs were used which were neither pregnant nor postpartum. Each dog was anaesthetised with intravenous pentobarbital (Nembutal^{R}) 30 mg per kg of body weight.

Under aseptic conditions, the bladder was catheterised and drained of urine. Two ureteric catheters were passed into the urethra and placed under X-ray fluoroscopy in its proximal and middle thirds to record pressures U1 and U2 respectively. These catheters had their ends amputated so that only a terminal orifice was used to record the pressure. They were also cut short to be 10 cm long, and were then sutured in place.

The catheters were attached to Statham[1] transducers (Model P23) which in turn were connected to a Grass[2] polygraph (Model 5D). To prevent the catheters adhering to the urethral wall they were connected to syringes driven by a Harvard infusion pump, which was adapted to deliver 1 ml of saline each hour through the terminal orifice of each recording catheter. This exerted negligible pressure on the transducers but was effective in preventing the eyes of the catheters adhering to the urethral wall.

Drugs were administered through a cannula in the external jugular vein. A second cannula was inserted percutaneously in the femoral artery, connected to a transducer and thence to the Grass polygraph.

4 other adult female dogs were anaesthetised and all catheters placed in an identical manner. Through a long midline incision the abdominal aorta was mobilised and occluded with a vascular clamp. After 5 minutes occlusion the clamp was released. The blood pressure in the femoral artery, and the urethral pressures U1 and U2 were monitored.

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[1] Statham Laboratories, Inc., Hato Rey, Puerto Rico.

[2] Grass, 101 Old Colony Avenue, Quincy, Massachusetts, USA.

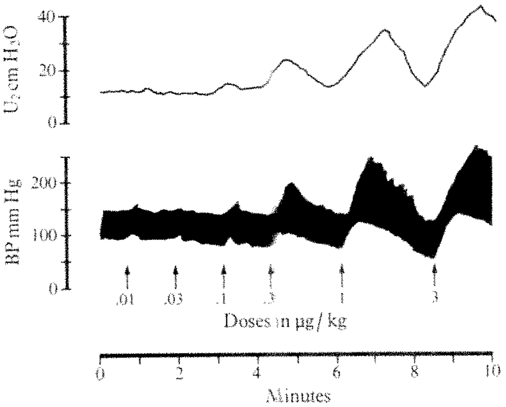

Fig. 1

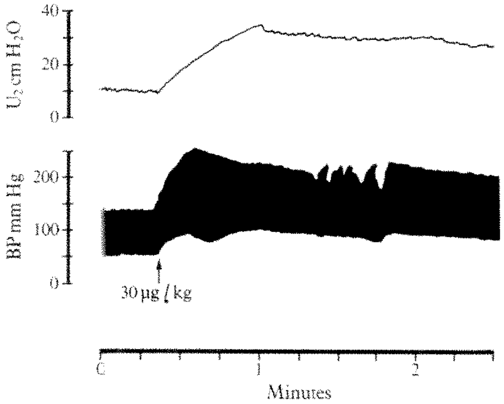

Fig. 2

Fig. 1. The effect of norepinephrine in increasing doses.

Fig. 2. The effect of norepinephrine. The BP rises synchronously with U2. After 15 seconds, the BP begins to fall, as compensatory mechanisms of the cardiovascular system take effect.

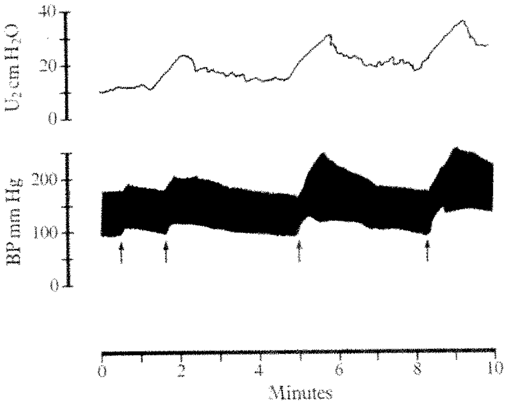

Fig. 3

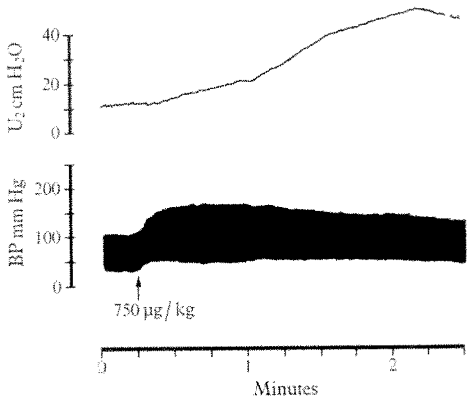

Fig. 4

Fig. 3. The effect of angiotensin in increasing doses.

Fig. 4. The effect of angiotensin. Although the BP rises immediately, the U2 rises after a 30 second delay and continues to rise after the BP has begun to fall.

Exsanguination was then achieved with a 16 needle in the abdominal aorta while simultaneously blood and urethral pressures were monitored.

Results

Effect of Norepinephrine

Increasing doses of norepinephrine produced increasingly greater responses of both blood and urethral pressures to a maximum at the identical dose (Fig. 1). The rises were seen in both U1 and U2, but were consistently greater in U2. The rises in U2 are coincident with the changes in blood pressure and the fall in U2 follows closely the fall in blood pressure (Fig. 2).

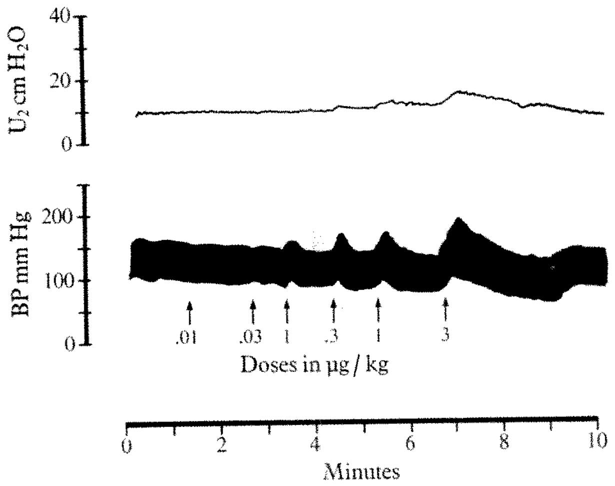

Fig. 5

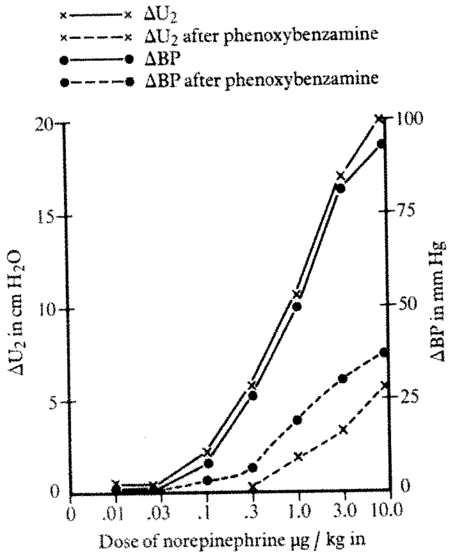

Fig. 6

Fig. 5. The effect of norepinephrine after phenoxybenzamine (10 mg/kg). There is a reduction in the responses of both BP and U2.

Fig. 6. Log dose response curve of norepinephrine before and after phenoxybenzamine. ΔBP and ΔU2 are the changes in BP and U2 pressures respectively.

Effect of Angiotensin

Increasing doses produced a maximum effect on both blood and urethral pressures, which were similar to the responses noted with norepinephrine (Fig. 3). However the maximum rise in U2 was consistently greater with angiotensin than with norepinephrine. The time sequence of the pressure changes is quite different (Fig. 4). The blood pressure rises immediately. This is then followed by the rise in U2 which slowly rises to a maximum. The blood pressure then falls but U2 continues to rise, only to begin to fall well after the blood pressure has passed its peak.

Effect of Norepinephrine after Phenoxybenzamine

Phenoxybenzamine hydrochloride (Dibenzyline^{R}) 10 mg/kg was then given intravenously. After a delay of 30 minutes doses of norepinephrine identical to the ones administered initially were given (Fig. 5). The increase in blood and intraurethral pressure response was markedly diminished with a shift to the right of the dose response curve (Fig. 6). When this was analysed statistically using the X square test, the shift of the dose response curve of both the blood pressure and U2 was highly significant ($P < 0{\cdot}0005$ with Yates correction factor for a 2 : 2 contingency table).

Effect of Angiotensin after Phenoxybenzamine

Angiotensin was then given in identical doses (Fig. 7) and the same blood pressure responses were noted as prior to blockade. However while the blood pressure did not alter significantly, the fall in U2 responses was highly significant ($P < 0{\cdot}005$). This is illustrated in the dose response curve (Fig. 8).

Effect of Aortic Occlusion

A small fall in U2 was noted. When the clamp was released there was a rise in U2 (Fig. 9). This rise tended to overshoot the previous resting level of U2 and then rapidly return to its previous

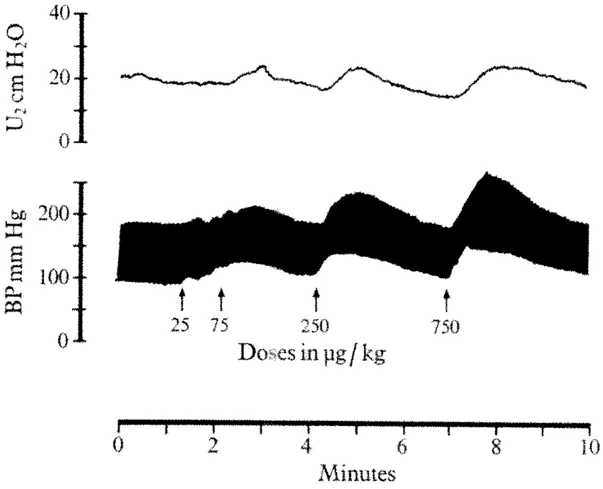

Fig. 7

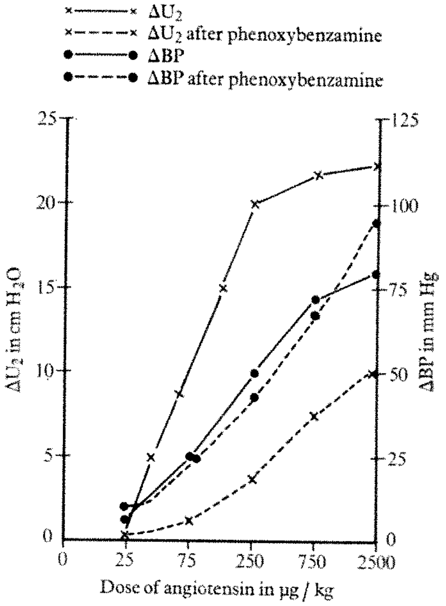

Fig. 8

Fig. 7. The effect of angiotensin after phenoxybenzamine (10 mg/kg). The BP elevation is not affected, but there is a reduction in the U2 elevation.

Fig. 8. Log dose response curve of angiotensin before and after phenoxybenzamine. The marked shift to the right of the ΔU2 curve after phenoxybenzamine is seen.

level. It was questioned whether this rise might be a reflex mediated through the α-division of the sympathetic nervous system, but this rise was not prevented by α-sympathetic blockade with phentolamine (Regitine^{R}) 0·5 mg/kg body weight.

Effect of Exsanguination

Again there was a small fall in intraurethral pressure, but there was still a resting pressure at the time of complete cardiac arrest (Fig. 10).

Discussion

If the elevation in intraurethral pressure following the administration of norepinephrine and angiotensin was caused indirectly by the constriction of the blood vessel within the urethral wall, the rise in blood pressure would parallel the rise in U2. Furthermore, one might expect the maximal rise in blood pressure to coincide with the maximal rise in U2. While this is found with norepinephrine, with angiotensin the maximal rise is delayed and reached after the blood pressure has already begun to fall; moreover, the beginning of the rise follows the initiation of the rise of the blood pressure, whereas with norepinephrine, both pressures rise simultaneously. This indicates that the angiotensin effect on the urethral wall is separate from its effect on the surrounding arterioles. Tanagho *et al.* (1969) believed that angiotensin is a pure vasoconstrictor. It is recognised that angiotensin acts indirectly through the sympathetic division of the autonomic nervous system or occasionally through the parasympathetic division (Goodman and Gilman, 1970). More important, angiotensin may also act on smooth muscle other than vascular smooth muscle; and rat colonic wall is used in its bioassay (Regoli and Vane, 1964).

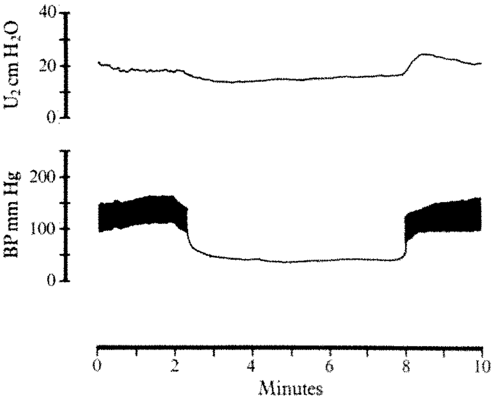

Fig. 9. Effect of aortic occlusion.

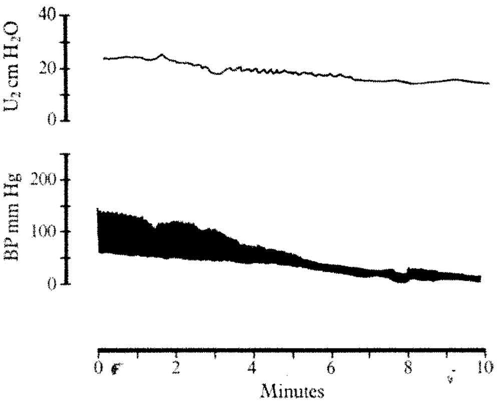

Fig. 10. Effect of exsanguination.

The alteration of intramural urethral pressure in response to angiotensin after α blockade is interesting. The shift to the right of the dose response curve (Fig. 8) demonstrates that it is partly mediated through the α-division of the sympathetic nervous system. That the pressure rise is not abolished indicates its direct action on urethral smooth muscle. Furthermore, the rise in U2 with supramaximal doses is greater with angiotensin than with norepinephrine. This view is supported by the studies of Raz, Zeigler and Caine (1972) who showed in urethral muscle strip experiments a reduction of the contractile response to angiotensin after α blockade. The blood pressure rise with increasing doses of angiotensin is unchanged after blockade whereas the U2 rise is reduced. This dissociation between blood pressure and U2 rise does not support the hypothesis that the sympathetic nervous system acts only indirectly through the surrounding blood vessels on the urethral pressure.

If the turgor of the blood vessels in the urethral wall played no part in the resting intramural urethral pressure, one would expect no change in the intramural pressure after aortic clamping. However, there is a small but definite fall during occlusion followed by a rise and overshoot when the clamp is released. This overshoot would be consistent with the rapid filling of the empty blood sinuses in the urethral wall. Raz *et al.* (1972) also carried out aortic occlusion experiments but recorded the urethral profile during occlusion without measuring the blood pressure. They observed a fall of the maximum urethral pressure of about one-third, but did not observe the overshoot phenomenon. The exsanguination experiments which show a small fall of U2 are confirming the minor contribution that vascular turgor makes to the resting intramural urethral pressure.

Enhörning (1961), who was the first to record vascular pulsations in the normal human female urethra, has shown that the amplitude of these pulsations ranged from 0 to 10 cm of water, whereas mean resting intraurethral pressure averaged 84 to 99 cm of water. Similar pulsations were also recorded in our experiments on dogs, which were abolished during aortic occlusion. It may be concluded that the vascular component is similar in both dog and man.

Summary

While there is a vascular component to intraurethral pressure, it is small. The changes noted in intraurethral pressure with sympathetic stimulation are mediated not through the changes in calibre of the blood vessels but directly on the smooth muscle of the urethra. Angiotensin causes a rise in intraurethral pressure; partly through a direct action on the urethral smooth

muscle and partly mediated through stimulation of the α-division of the sympathetic nervous system.

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Urethral Injury: A Retrospective Study

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Urethral rupture is an uncommon injury. Few surgeons treat a sufficient number of patients to be able to assess their own results. This retrospective study reports the results of treatment by a number of surgeons in non-specialist surgical units.

Patients Studied

A total of 63 patients who had suffered urethral injury were studied. They had received treatment in various hospitals in the Sheffield region, or had been referred to the Urological Unit, Sheffield, following the failure of their primary treatment. The average age of the patients was 32·3 years, and all were male. One female with this injury was excluded from the study, as she had suffered gynaecological and rectal injuries which complicated the treatment of her urethral injury. 3 patients sustained a bladder rupture in addition to their urethral injury.

The age of the patients at the time of injury, and the nature of their accident is shown in Figure 1. One-third of the patients (21) were aged below 20 at the time of their injury. 5 of the 8 patients below the age of 15 were pedestrians; 9 of the 13 aged 16 to 20 were involved in motor cycle accidents. At other ages no particular type of accident was prevalent, although a number of mining injuries was seen from the South Yorkshire and Derbyshire coalfield.

It was possible to follow-up 50 of the patients, either by interview, or by questionnaire, and the remainder of this paper refers to these patients.

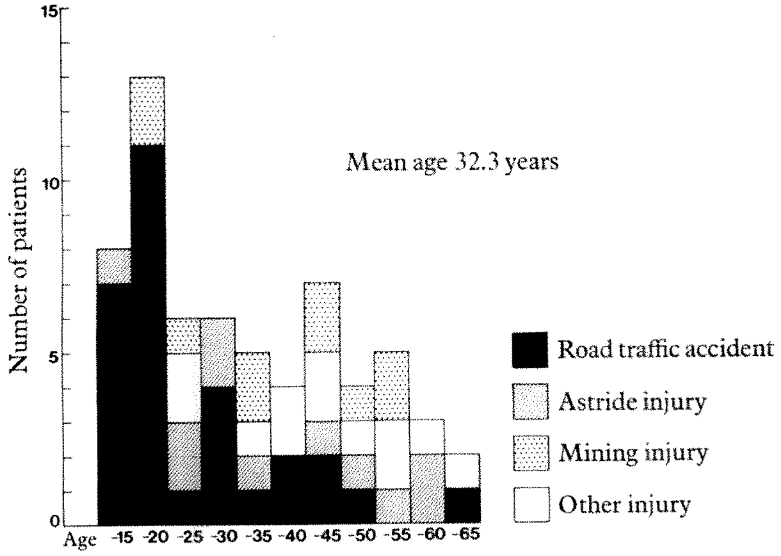


Fig. 1. Urethral injury: aetiology and age when injured (63 Patients).

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

Table I

Severity of Urethral Injury, and Follow-up Time
50 Patients

	< 2 years	2-5 years	5 years +
Minor injury 8 Patients	1	3	4
Incomplete rupture 14 Patients	0	1	13
Complete rupture 28 Patients	4	4	20

Table II

Primary Treatment for each Type of Injury
50 Patients

	Minor injury	Incomplete rupture	Complete rupture
Expectant	2	...	...
Urethral catheterisation	6	7	...
Suprapubic cystostomy	...	3	5
Railroaded catheter	...	4	23

Results

Severity of Injury. Patients were divided into 3 groups, depending upon the severity of their injury. Minor injuries, with mucosal damage only but no loss of the continuity of the urethra; incomplete ruptures, with partial disruption of the continuity of the urethra, and complete ruptures, where there was total loss of the continuity of the urethra.

The extent of the injury was assessed on the physical signs, urethrography, the inability to pass a catheter and the operative findings. Some originally incomplete ruptures may have been made complete by urethral instrumentation. These are classified as having sustained complete rupture.

The number of patients sustaining each degree of injury, and their follow-up time, is shown in Table I.

Primary Treatment (Table II). 2 of the 8 patients with minor injury were treated expectantly, both had passed blood-stained urine; the other 6 patients were catheterised.

Of the 14 patients with incomplete rupture, 7 were catheterised, 3 had suprapubic cystostomy alone, and 4 had a "railroaded" catheter. By "railroading" we mean the manipulation of a catheter across the urethral gap at open operation.

Where the rupture was complete, 23 had "railroaded" catheters, the remaining 5 suprapubic cystostomy alone.

Stricture Formation, Following Primary Surgery (Table III). The incidence of stricture formation in the minor injuries is high, the probable reason being failure to appreciate the possibility of strictures occurring, therefore these patients were not adequately followed up.

Table III

Primary Method of Treatment and Subsequent Stricture Formation

	No stricture	Stricture
Expectant	1	1
Minor injury 8 patients		
Urethral catheterisation	2	4
Incomplete rupture 14 patients		
Urethral catheterisation	3	4
Suprapubic cystostomy	1	2
"Railroaded" catheter	2	2
Complete rupture 28 patients		
Suprapubic cystostomy	0	5
"Railroaded" catheter	5	18

Table IV

Number of Patients who have required Urethroplasties, or Stricture Excision

Minor injury	No further surgery	5*
	Secondary surgery	3
Incomplete rupture	No further surgery	10
	Secondary surgery	4
Complete rupture	No further surgery	14
	Secondary surgery	14

* One patient awaiting urethroplasty.

With incomplete rupture, there are insufficient numbers to compare stricture formation rates with different methods of primary treatment. In those cases where it was possible to catheterise the urethra without open operation, there is as high a stricture rate as when a "railroading" technique had to be employed.

With complete rupture, there is a small number of patients in whom a stricture did not develop, and these had been treated with a "railroaded" catheter.

Of the 14 patients in this survey who have not developed a stricture, only 3 have been followed up for less than 5 years.

The number of patients requiring urethroplasty or excision of their stricture is shown in Table IV.

29 patients in the survey have not had further surgery following their primary treatment, but some still attend for bouginage (Table V).

4 of the 5 patients with minor injury, who have not required secondary surgery have satisfactory micturition, although one is being dilated. The other patient is awaiting a urethroplasty.

10 patients with incomplete rupture have not needed secondary surgery, 9 have satisfactory micturition, but 2 still attend for dilatation. The other patient is incontinent without a stricture.

14 of the complete ruptures have not required secondary surgery. Of these, 12 still have dilatations, 10 with satisfactory micturition. The other 2 are incontinent without strictures.

Table V

Frequency of Dilatation required in Patients without Secondary Surgery

	Frequency of dilatation			Number with satisfactory micturition
	<6/12	6/12 to 2 years	2 years+	
Minor injuries 5 out of 8	2	0	3	4 out of 5
Incomplete rupture 10 out of 14	0	2	8	9 out of 10
Complete rupture 14 out of 28	6	6	2	11 out of 14

Table VI

Site of Injury, and Stricture Formation

	Injury site	No stricture	Stricture
Minor injury	Membranous	1	1
	Bulbous	2	4
Incomplete rupture	Membranous	3	2
	Bulbous	3	6
Complete rupture	Membranous	5	14
	Bulbous	0	9

Site of Injury and Urethral Stricture (Table VI). There is a higher incidence of stricture formation after bulbous injury. Nearly 80% of bulbous injuries developed strictures, compared with 65% if the injury was membranous. With complete rupture all the bulbous injuries developed a stricture, against 70% if the site was membranous.

Assessment of Urinary Status. In order to assess the urinary status of these patients, taking into account nocturia, daytime frequency, strength of stream, hesitancy, straining and incontinence, we have given points for each of these symptoms. When added together, each patient has been given a score, and classified as having good, moderate or poor micturition (Table VII).

"Good" micturition must be almost normal, "moderate" is compatible with normal living and working conditions, and "poor" implies interference with normal life.

With this points system, we have compared the urinary status of patients following their primary treatment, and as they are at present, following any further definitive surgery. Those patients who had a suprapubic cystostomy, immediately followed by elective surgery, are assessed after this elective surgery (Fig. 2).

Half the patients (4) with minor injuries had poor micturition following their primary treatment, their present status is satisfactory (moderate or good) apart from 1 patient awaiting urethroplasty.

Following their primary treatment for incomplete rupture, 64·3% of the patients had satisfactory micturition; further surgery being needed in 4 of the 14 patients, bringing the satisfactory group up to 92·8%.

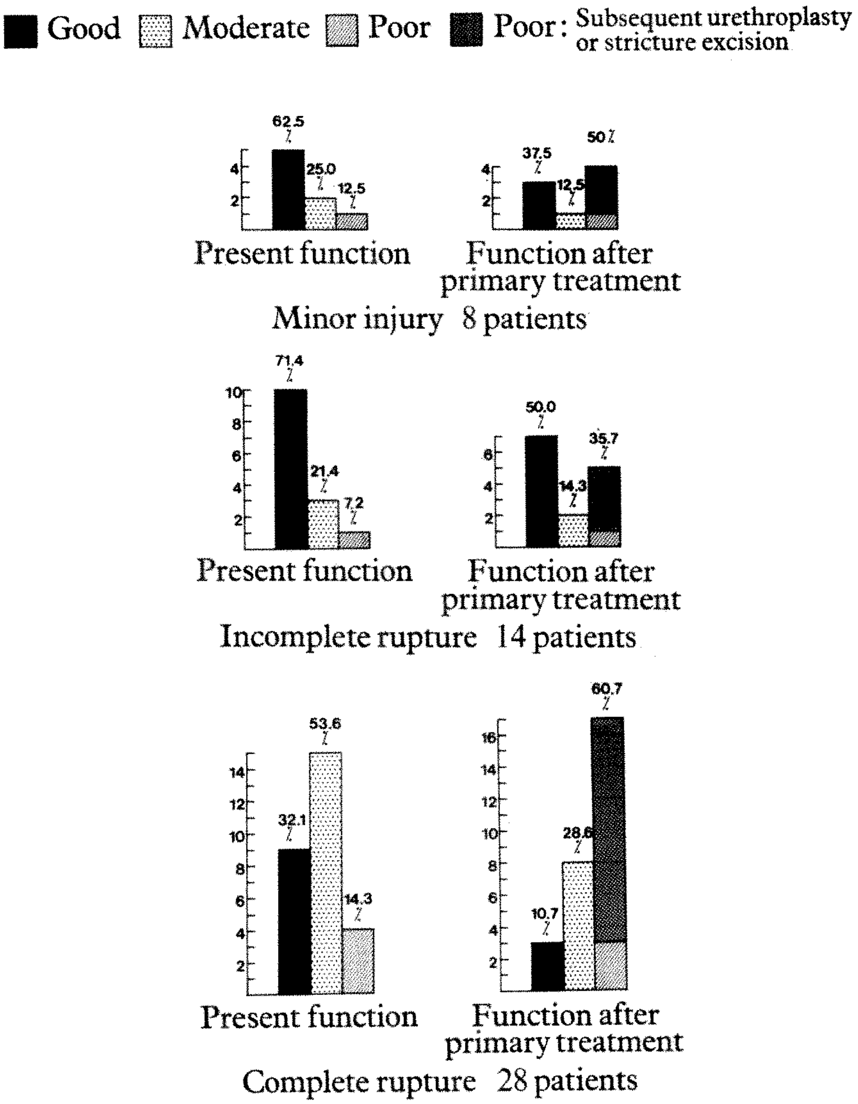


Fig. 2. Functional results following primary treatment and any secondary surgery.

Only 39·3% of the complete ruptures had satisfactory micturition following their primary treatment. This has been increased to 85·7% by secondary surgery in half (14) the patients.

Potency

Potency has been assessed on a similar points system to that of urinary status (Table VIII).

Patients with minor injuries remained potent with one exception, a man of 35, who also had severe pelvic fractures (Fig. 3).

Table VII

Assessment of Urinary Status

A points system is used to give each patient a score

Nocturia	Rarely	1-3 times	3 times
Points	0	1	2
Day frequency	3 hours	1-3 hourly	< 1 hour
Points	0	1	2
Stream	Good	Fair or poor	Dribble
Points	0	1	2
Hesitancy	Absent	Present	Marked
Points	0	1	2
Straining	Absent	Present	Marked
Points	0	1	2
Incontinence	Stress	Post-voiding	Urge
Points	1	1	1
Unconscious incontinence 4 Points			

A score of less than 3	*Good*
A score of 4 to 7 points	*Moderate*
A score of 8 or more	*Poor*

Table VIII

Assessment of Potency

A points system is used to give each patient a score

Erections	Yes	Sometimes	Partial	Never
Points	0	1	2	3
Ejaculation	Yes	Sometimes	No	
Points	0	1	2	
Intercourse	Yes	No		
Points	0	1		

A score of 0 or 1	*Potent*
A score of 2	*Partial impotence*
A score of 3 or more	*Impotent*

78·6% of the patients with incomplete rupture regained their potency. 2 of the 3 patients with impotence had suffered severe pelvic fractures; the other a penetrating perineal injury with a spike, involving the membranous urethra.

Only 32·1% of patients with complete urethral rupture remained potent after their injury.

The incidence of impotence was unaffected by the primary treatment.

Age when Injured and Potency (Fig. 4). There are too few cases of minor injury and incomplete rupture to show any age significance. When there is complete urethral injury, however, age is important. 7 out of 9 complete ruptures below the age of 25 remained potent, but only 2 out of 19 over this age.

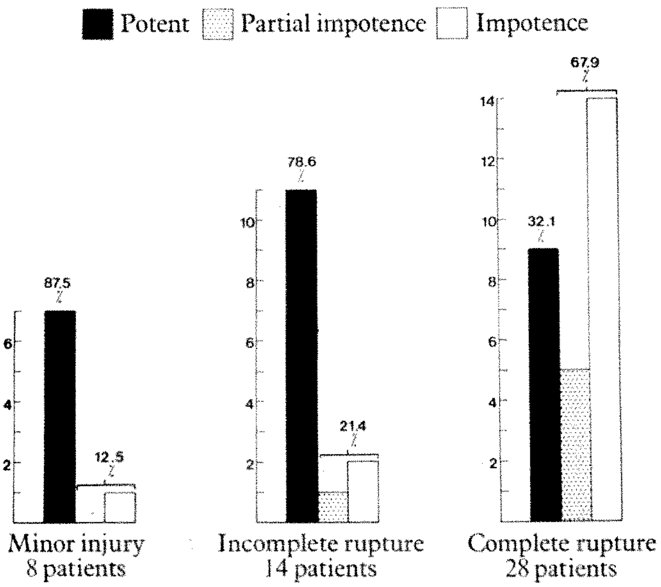


Fig. 3. Present potency, and degree of injury.

The potent patients in the survey were questioned separately by questionnaire, about the return of their potency after their injury. Replies being available from 18 of the 20 patients with incomplete and complete rupture. Potency had returned within one year of the injury, in the majority within 6 months (Table IX).

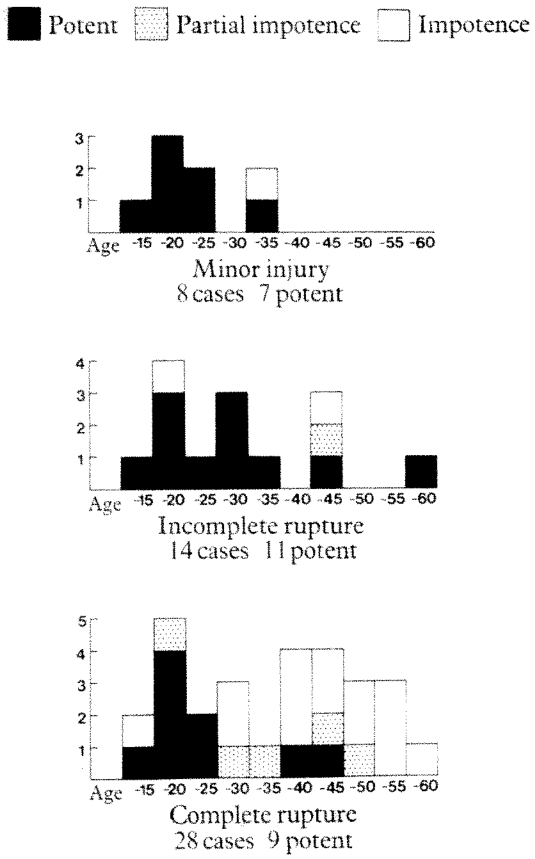
Fracture of the Pelvis and Impotence (Table X). Isolated instances of impotence may occur with minor injuries and incomplete ruptures, if the pelvis is fractured. If there is a fracture associated with a complete rupture, the impotence rate is 77·8% compared with 50% in patients without a fracture.

Site of the Urethral Injury, and Potency (Table XI). A membranous injury of any degree, has a higher risk of impotence than a bulbous injury of similar magnitude.

Incidence of late Urinary Tract Infections (Table XII). After any degree of urethral injury, there was a high incidence of recurrent urinary infections, 40% of all the patients being affected, 6% developing bladder or urethral calculi. 12% suffered from epididymitis at some time after their injury. One patient had a peri-urethral abscess.

Discussion

There is a higher incidence of complete rupture of the urethra in this survey, than in the Bristol series of Mitchell (Mitchell, 1968). Patients have been included in the survey, whose primary treatment had failed, and were referred to a urology unit for secondary surgery. Most of these had complete urethral rupture. In a retrospective survey, some patients with successful treatment for minor injuries and incomplete rupture have been lost to follow-up, and therefore not included.



Minor injury
8 cases 7 potent

Incomplete rupture
14 cases 11 potent

Complete rupture
28 cases 9 potent

Fig. 4. Age when injured, degree of injury and present potency.

Some cases of incomplete rupture may have been converted into complete rupture by urethral instrumentation, as has been described by Mitchell (Mitchell, 1968, 1971).

Many of the road traffic accidents in this survey were pedestrian or motor cycle crushing injuries, rather than impact passenger injuries. A crush injury being more likely to cause a complete rupture (Mitchell, 1968).

The diagnosis of ruptured urethra was obvious when the triad of urethral bleeding, the inability to pass urine, and a palpable bladder was present. Some minor injuries did not have this triad, but their presence was suspected as there had been trauma. Failure to follow up these minor injuries allowed serious strictures to develop insidiously.

Careful rectal examination of the prostate must be made in every suspected case, and the seriousness of the high "floating" prostate appreciated. Although this is generally recognised, a written note of rectal findings was made in only 6 cases in the present survey, by the admitting medical officer!

Urethrography, whilst not always distinguishing between complete and incomplete ruptures, confirms the diagnosis, and establishes the site of the injury. We feel that this is preferable to blind urethral instrumentation as the first step in the evaluation of suspected cases.

When an incomplete rupture could be treated by primary catheterisation, we would have expected a lower incidence of stricture formation, than when a catheter had to be passed at

Table IX

Interval between Injury, and Return of Potency

Incomplete rupture	9 cases of original 11 potent
Immediately	3
Within 6 months	4
Within 1 year	2
After 1 year	0
Complete rupture	9 cases of original 9 potent
Immediately	2
Within 6 months	6
Within 1 year	1
After 1 year	0

Table X

Fracture of the True Pelvis, and Incidence of Impotence, Partial or Total

Minor injury	No fracture	Potent	2	100·0%
		Impotent	0	0·0%
	Fracture	Potent	5	83·3%
		Impotent	1	16·7%
Incomplete rupture	No fracture	Potent	4	80·0%
		Impotent	1	20·0%
	Fracture	Potent	7	77·8%
		Impotent	2	22·2%
Complete rupture	No fracture	Potent	3	50·0%
		Impotent	3	50·0%
	Fracture	Potent	6	22·2%
		Impotent	16	77·8%

Table XI

Site of Urethral Injury, and Incidence of Impotence, Partial or Total

Minor injury	Membranous	Potent	1	50·0%
		Impotent	1	50·0%
	Bulbous	Potent	6	100·0%
		Impotent	0	0·0%
Incomplete rupture	Membranous	Potent	3	60·0%
		Impotent	2	40·0%
	Bulbous	Potent	8	88·9%
		Impotent	1	11·1%
Complete rupture	Membranous	Potent	5	26·3%
		Impotent	14	73·7%
	Bulbous	Potent	4	44·4%
		Impotent	5	55·6%

Table XII

Incidence of Urinary Tract Infections, and Calculus Formation

Minor injury	No infections or calculi	2	25·0%
	Recurrent infected urine	5	62·5%
	Epididymitis	2	25·0%
	Peri-urethral abscess	1	12·5%
	Calculi	0	0·0%
Incomplete rupture	No infections or calculi	11	78·6%
	Recurrent infected urine	2	14·3%
	Epididymitis	1	7·1%
	Calculi	1	7·1%
Complete rupture	No infections or calculi	13	46·4%
	Recurrent infected urine	13	46·4%
	Epididymitis	3	10·7%
	Calculi	2	7·1%

open operation; but this was not so. This unexpected finding may be related to the fact that the "railroaded" catheter was left in for at least 3 to 4 weeks, but when a catheter could be passed urethrally, it was removed much earlier. It has been shown by Weaver and Schulte, that urethral epithelium healed in about 10 days, but that a minimum of 3 weeks was necessary for corpus spongiosum regeneration, in canine experiments (Weaver and Schulte, 1962).

"Railroading" a catheter is the usual practice in many centres, and various adjunct measures are used to prevent stricture formation.

In a series of 22 patients, De Weerd treated 18 with a "railroaded" catheter with added traction (De Weerd, 1957). Only 2 required secondary surgery; but some were incomplete ruptures, and follow-up time was limited. The need for 4 to 6 weeks' catheterisation with initial traction, at an angle of 45° to 60° was stressed.

The importance of close approximation of the torn urethral ends, without interposing tissue is emphasised by Pierce (1972). Suprapubic exploration of ruptures, with division of the symphysis pubis, showed a gap of 1·5 to 4 cm, which could not be reduced by traction alone (Ragde and McInnes, 1969). They recommended active mobilisation of the vesical neck and prostate to achieve approximation, and allow direct suture of the torn urethral ends. Apical prostatic sutures brought out through the perineum have been used by Young and Davies (1926).

In the present series, 5 out of 13 patients with complete membranous rupture treated with a "railroaded" catheter did not develop a stricture, 4 of these having been followed-up for more than 5 years, one for 4 years. Other series have shown that stricture is not always the outcome with complete rupture, when a "railroaded" catheter is employed (Villar, Ireland and Cass, 1969; Pierce, 1972; and Ragde and McInnes, 1969).

We were unable to assess the value of traction in this survey.

Very few patients were treated by suprapubic cystostomy alone; the strict criteria of Mitchell (1968) were not applied, and the results should not be interpreted as those of this specified methods of treatment. The 5 cases of complete rupture treated by this method all did badly; this may reflect initial instrumentation, or technical problems at the time of the delayed elective surgery. Using delayed elective urethroplasty, Morehouse, Belitsky and Mackinnon (1972) had no cases of stricture formation in 11 patients. From the present survey, it seems that once suprapubic drainage has been established, it is advisable that patients be referred to a centre experienced in urethral surgery, if the best results are to be obtained.

The incidence of impotence after urethral injury varies widely in different series, from "over a quarter" (Waterhouse and Gross, 1969), to 42% in cases of complete rupture (Gibson, 1970). The incidence in the present series of 67·9% in complete rupture, is very high. Our patients had been followed-up for sufficient time for impotence to recover, that is more than 4 years (Gibson, 1970). We have found that all the patients who regained their potency did so within one year.

Mitchell found an age difference in the effect of the injury on potency (Mitchell, 1968), he grouped his patients above and below the age of 40. We have found that there is an age difference above and below the age of 25 years.

The incidence of urethral injury in fracture of the pelvis varies widely in different series; from 0·7% to 17·3%, (Kaiser and Farrow, 1965). Three patients in the present series were amongst 271 cases of fracture of the pelvis in a 10-year period, who received their orthopaedic treatment in Sheffield, an incidence of 2·6%.

Summary

In a retrospective survey of urethral injury 50 patients out of 63 have been followed-up by interview and questionnaire.

No real advantage was found between primary treatments in the initial management of minor injuries or incomplete ruptures, although stricture formation is common.

50% of the complete ruptures treated by "railroaded" catheter had acceptable micturition, although periodic dilatation is still required in the majority. In this survey, all those patients with complete rupture treated by suprapubic cystostomy required secondary surgery.

There is a high incidence of stricture after complete rupture of the bulbous urethra, regardless of the primary method of treatment.

Urethroplasty or stricture excision was required in 20 cases in the survey, 16 of the others still attend for dilatation, and 14 have had no treatment for more than 2 years, 12 with satisfactory micturition.

Impotence occurred mainly when there was a complete rupture, in patients over the age of 25. The incidence of impotence was higher if the rupture was membranous, and if there was a pelvic injury, and was uninfluenced by the primary treatment.

There is a high incidence of urinary tract infections following any urethral injury.

We wish to acknowledge the assistance given to us by the patients in this study, and the surgeons of Sheffield, Derby, Mansfield and Rotherham who have allowed us to include their patients in this survey. The Department of Medical Photography, The United Sheffield Hospitals, provided invaluable help in the preparation of the tables and figures.

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Experience with Treatment of Primary Malignant Disease of the Prostate by Localised External Supervoltage Irradiation using Cobalt-60 or High Energy Electrons

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In recent years a number of reports have been published from countries outside the United Kingdom describing the treatment of carcinoma of the prostate by an external source of supervoltage irradiation (Bagshaw, Kaplan and Sagerman, 1965; Del Regato, 1967; Grout *et al.*, 1971). This paper describes the clinical progress of a group of patients with prostatic neoplasms who were treated by external supervoltage therapy in the Radiotherapy Unit at St Luke's Hospital, Guildford, between the years 1968 and 1973 using either a cobalt-60 source or high energy electrons from a Betatron.

Clinical Material

The patients, 58 in all, were referred to St Luke's Hospital by a total of 12 Consultant Surgeons from 10 hospitals in the South West Metropolitan area. The ages of these patients ranged from 47 to 81 years, with a mean age of 68 years, at the time of referral (Fig. 1). The duration of their symptoms ranged from 7 days to 3 years, with an average of 9 months (Fig. 2), and these

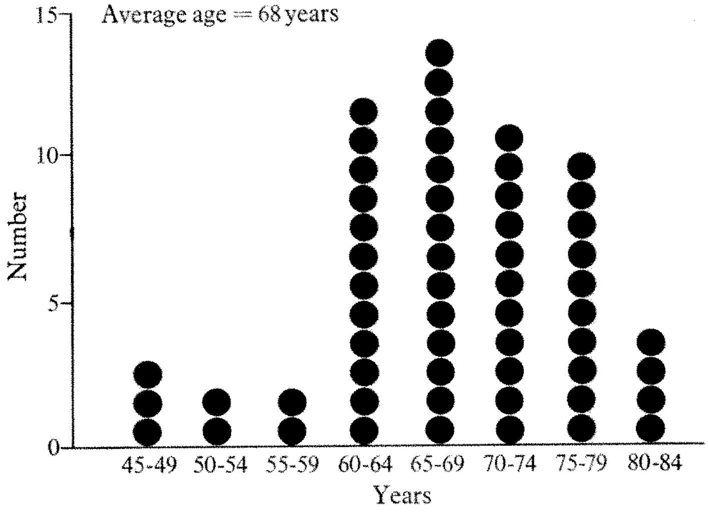

Fig. 1. Ages of 58 patients with primary malignant disease of the prostate at the time of referral for treatment.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

symptoms included the onset of frequency of micturition, a poor urinary stream, hesitancy, terminal dribbling and nocturia. In only 7 patients was haematuria among the presenting symptoms, but 19 were admitted as emergencies with acute retention of urine.

Because patients were referred to the Regional Radiotherapy Centre from 10 different surgical units no standard system of investigation was used, but investigations included physical examination, acid phosphatase estimations, skeletal surveys, intravenous urography and bone scanning. In 54 patients the diagnosis was confirmed by an initial operative procedure (Table I), 1 patient was considered not fit enough for any procedure requiring a general anaesthetic, 1 other required 8 operative procedures before the correct diagnosis could be established and in 2 no comment on the prostatic histology can be found in the notes. In 41 of the 58 patients an attempt at

Table I

Initial Operative Procedure to Confirm the Diagnosis of Malignant Disease of the Prostate

Trans-rectal biopsy	7
Trans-urethral resection	28
Retropubic prostatectomy	19
Total	54

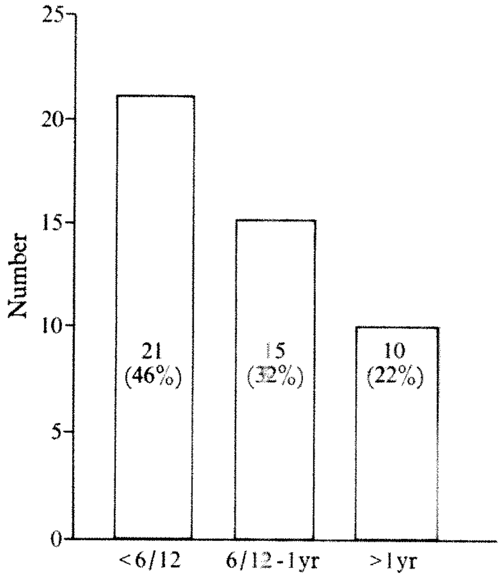

Fig. 2

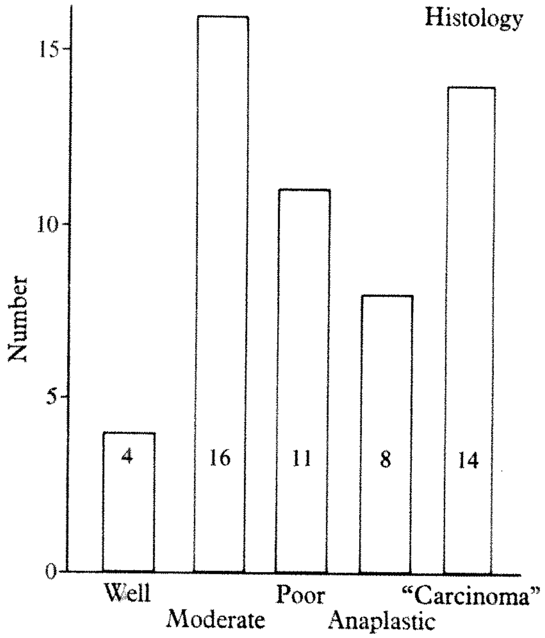

Fig. 3

Fig. 2. Duration of symptoms prior to referral of 58 patients with primary malignant disease of the prostate.

Fig. 3. Histological grading of tumour in 58 patients with primary malignant disease of the prostate.

cytological grading was made (Fig. 3). 2 of the prostatic tumours were found to be leiomyosarcomas and on 2 occasions the prostate itself was reported as being benign, but carcinoma apparently originating from the prostate was discovered in an adjacent lymph node and a biopsy of the prostatic capsule respectively.

A simple form of clinical staging was used (Fig. 4). Stage A represents a malignant tumour discovered after removal of a clinically benign gland; Stage B a palpable tumour completely confined to the prostate; Stage C_1 and C_2 represent tumours extending beyond the confines of the prostate by a distance of less than 6 cm and greater than 6 cm respectively without distant metastases. Stage D implies the presence of known metastatic disease.

When first seen 19 patients (34%) were considered to have a benign enlargement of the prostate and 24 (43%) were suspected of having a carcinoma confined to the gland (Stage **B**). 12 patients (22%) were clinically in Stage C and 1 in Stage D. This clinical staging was not upheld at the time of a subsequent operative procedure in 25 of the cases (47%). This high incidence of under-staging is familiar from other series (Whitmore, 1963; Belt and Schroeder, 1972) and Flocks (1973) emphasised that all attempts at clinical staging are subject to correction. He noted that 5% of Stage A tumours of the prostate involve either vascular or lymphatic lesions while in Stage B and C tumours 45% have lymphatic metastases and 10% have vascular metastases. This may be underlined by the finding in the present series that extra-capsular spread of malignant disease was found in 4 patients thought to have benign glands on clinical grounds.

All but 8 of the patients with an adenocarcinoma of the prostate were started on stilboestrol immediately after the diagnostic procedure. Doses ranged from 5 mg t.d.s. to 100 mg t.d.s., depending upon the beliefs of the surgeon who established the diagnosis. 13 (26%) of those

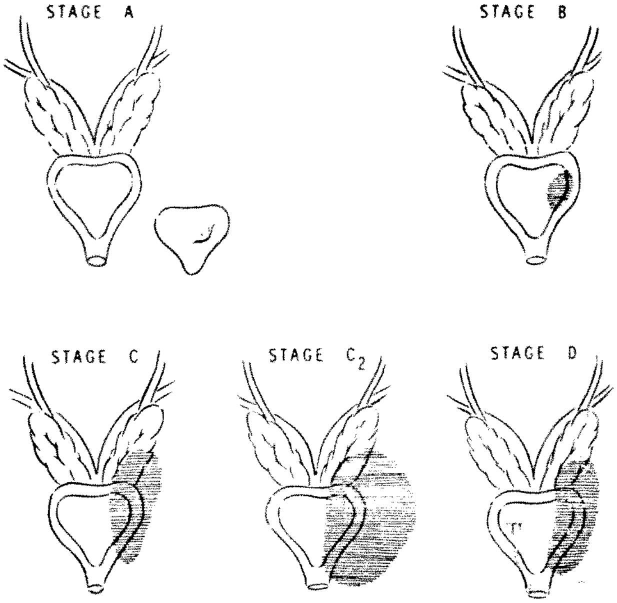

Fig. 4. A method of staging of malignant disease of the prostate:
Stage A: tumour discovered in a clinically benign prostate.
Stage B: tumour confined to the prostate.
Stage C_1: tumour arising from the prostate with extension less than 6 cm from the prostate without distant metastases
Stage C_2: tumour arising from the prostate with extension greater than 6 cm from the prostate without distant metastases.
Stage D: tumour of the prostate with metastases.

who commenced stilboestrol experienced side effects from the drug. Of the 55 patients in whom a histological diagnosis had been made 38 commenced a course of radiotherapy within 6 weeks of the initial procedure. The remaining 18 remained on hormonal therapy for periods ranging from 6 months to 7 years after the original diagnosis had been established, the change to irradiation therapy being either inability to tolerate oestrogens (7 patients) or evidence of local recurrence of disease (11 patients).

Radiotherapy Techniques

34 patients were subjected to irradiation from a cobalt-60 source and 23 were treated on the Betatron. One patient was treated by both methods. Before commencing treatment planning measurements were made by means of a technique of cystography and skin markers.

25 patients treated with cobalt-60 were exposed to a maximum tumour dose of 6,000 rads in six weeks, those with more locally advanced tumours receiving a relatively smaller dose to a larger tumour volume. In most cases an anterior arc technique was used. In the 23 patients treated with high energy electrons from the Betatron a direct perineal field was used and the multiple fractionation regimes were designed to give a dose biologically equivalent to the 6,000 rads in 6 weeks given by the Cobalt Unit.

Complications of Treatment

These are summarised in Tables II and III for cobalt-60 and Betatron irradiation respectively. It can be seen that the high energy electrons produced a much higher incidence of skin reactions and in 11 patients this was sufficiently severe to interrupt treatment for periods of 5 to 14 days. In addition 3 treatments had to be stopped early because of extreme skin discomfort. By contrast the cobalt treated patients suffered little in this respect. All skin reactions were treated with locally applied betamethasone and subsided completely, although in the severe cases this took up to 18 months.

Dysuria and frequency was not a problem with the Betatron therapy, the more severe symptoms appearing during cobalt irradiation in which group 1 patient ultimately developed a small capacity fibrotic bladder.

The incidence of troublesome diarrhoea in both groups was much the same and usually this responded to mist. kaolin and morph. in the mildly and moderately severely affected patients. Radiation proctitis developed in 3 of the patients receiving cobalt therapy. 2 responded to Predsol enemata, but the third man, who had extensive bony metastases, was subjected to a de-functioning colostomy in a vain effort to prevent his death from an uncontrollable rectal haemorrhage. The Betatron group did slightly less well in this respect, 6 patients developing radiation proctitis 6 to 11 months after treatment and 2 of these were so severe as to necessitate a de-functioning colostomy. In both these patients the multiple fractionation regime consisted of large doses 3 times a week and after this experience a smaller, more frequently applied dose technique was adopted.

Temporary acute retention of urine occurred in 3 patients during Betatron therapy, 2 associated with urinary infection.

The patient receiving a combination of cobalt and Betatron therapy suffered a moderately severe skin reaction, troublesome frequency of micturition and diarrhoea and subsequently developed a radiation proctitis.

Results

58 patients were studied and 24 remain alive, 33 are dead, 1 patient having emigrated and being lost to follow-up (Table IV).

Table II

Side Effects Experienced During Treatment to a Malignant Disease of the Prostate using a Cobalt-60 Source

Complications of treatment—Cobalt-60	
Skin reactions	3 (12%)
2 mild	
1 moderate	
Dysuria and frequency	8 (32%)
6 mild	
1 moderate	
1 severe	
—1 developed a contracted bladder	
Diarrhoea	11 (44%)
8 mild	
3 moderate	
—3 developed a radiation proctitis	
—1 required a de-functioning colostomy	

Table III

Side Effects Experienced During Treatment to a Malignan Disease of the Prostate using High Energy Electrons from the Betatron

Complications of treatment—Betatron	
Skin reactions	23 (91%)
3 mild	
13 moderate	
4 severe	
Dysuria and frequency	4 (18%)
Diarrhoea	9 (40%)
6 mild	
3 moderate	
—6 developed a radiation proctitis	
—2 required a de-functioning colostomy	

Of the 33 dead patients 11 (19% of the series) died from other causes (Table V), their average age at the time o treatment being 72 years. 8 patients remained free of symptoms from their prostatic disease. 1 developed bone pains 2 months before dying of a myocardial infarction 19 months after completion of therapy. 1 man developed a carcinoma of the rectum 18 months after treatment and underwent an abdomino-perineal resection of the rectum before dying of hepatic metastases from his rectal growth. The eleventh patient had multiple bony metastases at the time of his death from uncontrollable rectal haemorrhage from an irradiation proctitis 16 months after treatment.

22 of the deaths were due to malignant disease of the prostate, 20 adenocarcinomas and 2 leiomyosarcomas. Total survival in this group after completion of radiotherapy ranged from 8 months to 44 months with an average of 14 months. 10 patients were treated on the Betatron and 12 on the Cobalt Unit. Both sarcomas did badly, dying within a year of treatment.

Table IV

Survival of 58 Patients Treated by External Beam Radiotherapy for Primary Malignant Disease of the Prostate

Alive	24 (41·5%)
Death from tumour	22 (36%)
Death from other cause	11 (19%)
Lost to follow-up	1 (0·5%)

Table V

Deaths from Other Causes in 58 Patients Treated by External Beam Radiotherapy for Malignant Disease of the Prostate

Myocardial infarction	5
Pneumonia	3
Pyelonephritis	1
Haemorrhage	1
Carcinoma of rectum	1

In the 20 patients dying of adenocarcinoma of the prostate 10 had good evidence of spread of the disease beyond the confines of the prostate at the time of treatment. Here the average survival ranged from 3 to 16 months with an average of 7½ months. Some symptom-free period was gained in 7 of the 10 and ranged from 1 to 7 months with an average of 2½ months only. All 7 had local control of their disease until death from metastatic disease. No local control was achieved in 3 cases, 2 Stage D and 1 Stage C_2 at the commencement of treatment, all died within 4 months of the completion of therapy.

Of the remaining 10 men the average survival period ranged from 9 months to 4 years, averaging 2 years. All gained a limited symptom-free period which ranged from 4 to 24 months, averaging 12 months. Local control of the disease was achieved until death in all but one of these patients, but 4 had complained of symptoms of a moderate radiation proctitis. 7 subsequently developed symptoms from bony metastases while 2 developed hepatic metastases and another succumbed to cerebral metastases.

24 patients remain alive, their survival period ranging from 7 months to 5½ years after radiotherapy, with an average of 2 years 10 months. Their ages at the time of treatment ranged from 52 to 80 years with an average of 67 years. 9 of these patients were treated on the Betatron and 15 on the Cobalt Unit. The average survival of each group is at present 3 years 11 months on the Betatron and 2 years 3 months on the Cobalt Unit.

Only 1 patient had evidence of metastatic disease at the commencement of treatment, bony secondaries after 7 years of treatment with stilboestrol for a well-differentiated adenocarcinoma. He remains well 14 months after radiotherapy and a sub-capsular orchidectomy, obstruction to the left ureter having resolved. Of the remainder 14 were clinically Stage B, 8 were clinically Stage C_1 and 1 was not recorded.

16 of the survivors are at present symptom free, but 1 of these required a course of local radiotherapy to a metastasis in his cervical spine 1 year ago. 1 man developed a lymphosarcoma; he has long since rejected the advice of doctors, doses himself with large quantities of Vitamin C and remains very well.

8 survivors have symptoms, but in only 1 man is this due to malignant disease having developed bony metastases 1 year after cobalt therapy to an anaplastic carcinoma of the prostate. The remaining 7 men are free of symptoms directly related to their original disease, but 4 have a residual radiation proctitis (1 having required a de-functioning colostomy). The other 3 have urinary symptoms, 1 with disabling frequency from a contracted bladder, another has an anterior urethral stricture and the last has remained incontinent of urine since his original trans-urethral resection of the prostate.

Excluding the 2 patients with sarcomas, 50 of the 56 patients were at some time treated with stilboestrol. 13 patients (26%) experienced side effects of this drug. 19 patients (80%) of the 24 patients still alive were able to stop oestrogens after the radiotherapy and remain well although 3 underwent a sub-capsular orchidectomy when the stilboestrol was stopped. 2 patients (8%) were never on any form of hormonal therapy.

Discussion

Pasteau and Degrais (1913) were the first to attempt treating prostatic cancer by irradiation when in 1913 they introduced radium into the bladder neck by means of a catheter. 9 years later while others were reporting their experiences of similar techniques (Bugbee, 1921; Bumpus, 1922; Deming, 1922; Young, 1922), it became apparent that whilst most tumours responded by some reduction in size many patients already harboured distant metastases from which they soon succumbed. In addition the severity of the accompanying radiation damage to the adjacent bladder and bowel made this form of therapy unacceptable.

With the advent of hormonal therapy in 1941 (Huggins, Scott and Hodges, 1941) attention turned away from the use of irradiation until 1952 when Flocks *et al.* described a method of treatment of carcinoma of the prostate by interstitial radiation with radioactive gold. Eventually its use became accepted in conjunction with sub-total or total prostatectomy and excellent results have been described (Carlton *et al.*, 1972).

The same decade which saw the advancement in the use of interstitial irradiation also witnessed the installation of teletherapy Cobalt-60 units and various high energy generators including linear accelerators and Betatrons. These new machines, capable of administering supervoltage irradiation, overcame some of the objections raised against the older forms of external beam therapy as the skin sparing property of the beam together with a better penetration and reduced side scatter resulted in a reduction in the severity of skin reactions and a lessening of the damage to adjacent viscera. Other benefits of using an external beam source as primary treatment may apply, the miserable side-effects of incontinence and impotence which may attend radical operative forms of treatment may more easily be avoided and the increased cardio-vascular morbidity and unpleasant side-effects of hormone treatment do not obtain (Veterans Administrative Co-Operative Research Group, 1967).

In this series irradiation was used primarily in an attempt to control the local disease and where possible oestrogens were stopped at the completion of treatment. It was felt by the authors that by this means the quality of survival of patients in an elderly age group could best be improved. Previous experience in treating prostatic tumours has indicated that in order to achieve ablation of the tumour a cumulative dose of around 6,000 R should be delivered to the tumour-bearing area (Flocks *et al.*, 1952; Carlton *et al.*, 1972). Whilst other methods have sought to divide this dosage between interstitial and external beams sources an external beam source alone has been used in this instance. Inevitably side-effects have resulted, with an incidence of damage to the adjacent bowel, bladder and overlying skin which is in keeping with the experience of other authors (Phillips and Lattimer, 1972). On the whole these complications have been short-lived although 3 patients required a de-functioning colostomy and 1 of these died as a direct result of irradiation damage. In this series, as in others (Rubin, 1969; Flocks, 1973), no good relationship has been observed between irradiation responsiveness and histological grading of the tumour.

In presenting these 58 patients it is appreciated that it is difficult to draw meaningful conclusions from a small series and it is also understood that the effects of irradiation may have been obscured by the fact that most patients began hormonal treatment a short time before irradiation commenced.

The follow-up of patients after treatment has usually been confined to an assessment of symptomatology and a palpable assessment of the prostatic size and consistency, which is notoriously inaccurate. No patient was subjected to a routine post-irradiation biopsy and not all had follow-up acid phosphatase estimations or skeletal survey. While the data presented does little to resolve the confusion surrounding the treatment of this form of malignant disease it is nevertheless our strong impression that external beam supervoltage irradiation will have an increasingly important part to play in the definitive and palliative treatment of carcinoma of the prostate.

Summary

58 patients with prostatic neoplasms were treated in the Radiotherapy Unit at St Luke's Hospital, Guildford, between the years 1968 and 1973. 54 had been subjected to a preliminary operative procedure and 50 were treated with stilboestrol before irradiation commenced.

34 were subjected to irradiation from a cobalt-60 source and 23 were treated on the Betatron. 1 patient was treated by a combination of both methods.

The results of these treatment methods have been examined and the complications of treatment encountered have been outlined.

These patients were treated by Dr H. Mellor and Dr W. F. White at St Luke's Hospital, Guildford. They were referred by Messrs J. Bull, T. J. Davenport, A. Eley, W. G. Gill, R. B. McGrigor, R. G. Notley, N. Pitt, S. C. Raw, F. A. W. Schweitzer, M. J. Solan, K. W. Wilkinson and P. J. M. Wright.

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Lengthening of the Congenital or Acquired Short Penis

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Congenital shortness of the penis, in association with dorsal chordee, is most commonly found with epispadias, either alone or in association with bladder exstrophy. Correction of the chordee requires that additional skin is brought to the penile dorsum and that the urethra, or in cases of epispadias with bladder exstrophy the urethral strip, is freed from the underlying corpora cavernosa so that it can retract proximally and its bow-string effect is eliminated.

The shortness of the penis in these patients is largely due to the separation of the pubic bones. The corpora cavernosa themselves are of adequate length but much of the length is wasted since it lies between the penile shaft and the bony attachment. Approximation of the pubes by iliac osteotomies, whilst possible, does not increase the length of the penis. Correction of the skeletal anomaly leads to a tilting of the pelvis; the ischial tuberosities move backwards, the pubo-ischial rami come to lie more horizontally and the penis retracts and becomes even less prominent than before. Lengthening of the corpora is best obtained by dissecting from above through a V incision and partially detaching the crura of the penis from the bone.

The mobilised crura allow the extra-penile portions of the corpora cavernosa to be advanced and approximated and so contribute to the length of the shaft (Fig. 1). I have not attempted to detach the crura entirely from the bone as has been described by Kelley and Eraklis (1971).

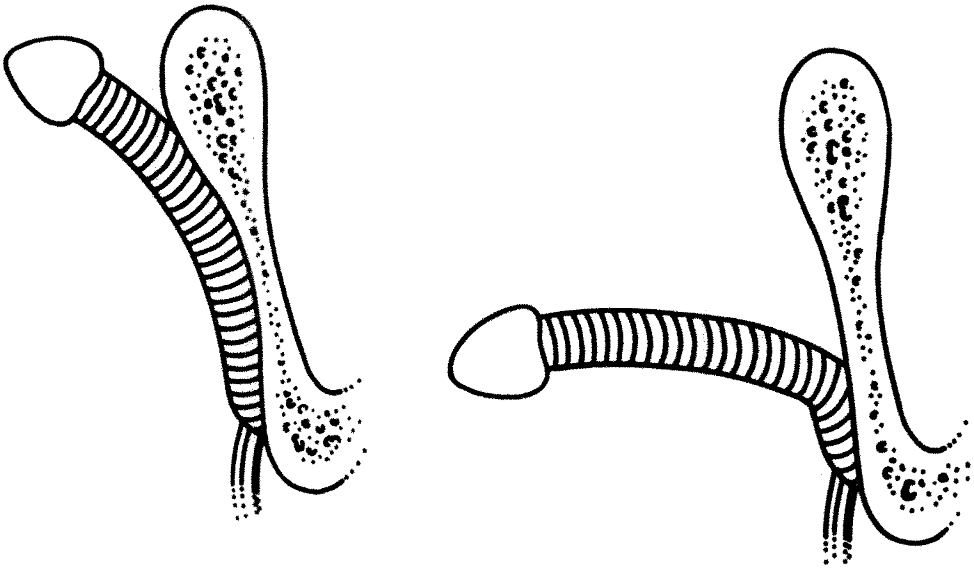

Fig. 1. Diagrams of vertical section through pubo-ischial ramus and penile crus in epispadias. *Left*, Short penile shaft. *Right*, Lengthening of shaft obtained by partially detaching the crus from the bone.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

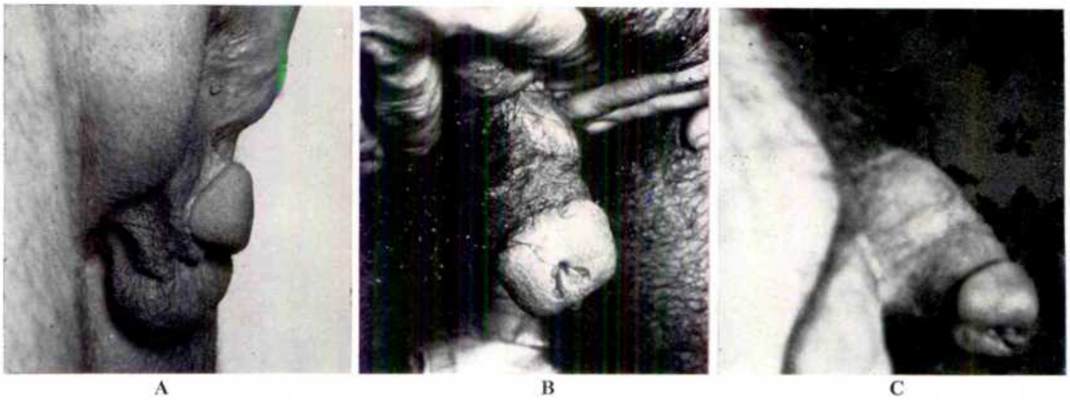

Fig. 2. Genitalia of man of 27 years who had bladder exstrophy treated by cystectomy and uretero-sigmoidostomy in early childhood. **A**, Before penile lengthening. Very short penis. **B**, After lengthening of penis. **C**, Photograph of erect organ taken by patient.

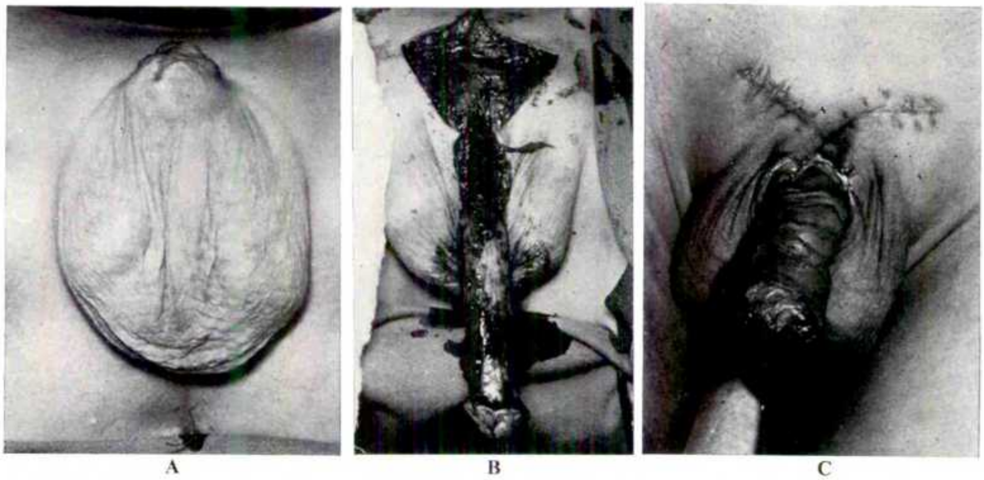

Fig. 3. Genitalia of boy of 10 years whose penile shaft sloughed following the misuse of diathermy during circumcision in infancy. **A**, Before lengthening. Virtually no penile projection. **B**, During operation. Good length obtained following partial detachment of crura from bone. The shaft was covered by a split skin graft. **C**, Appearance 3 months after operation.

This procedure would appear, from my experience, to carry an appreciable risk of denervating or devascularising the penis by damaging the neurovascular bundle entering the extremity of the crus, and in the majority of cases sufficient lengthening can be achieved without it.

There are several possible means of providing skin cover for the lengthened phallus. Firstly, penile skin may be used. The redundant ventral prepuce is invaluable here. When its two layers are separated the additional skin obtained may allow the penile skin to be sutured longitudinally on the dorsum of the organ. Alternatively, a flap formed from the prepuce may be swung to the dorsum, the glans being passed through a button-hole. If there is insufficient penile skin for either of these methods, the shaft may be buried under the front wall of the scrotum. After 3 months it is freed, at which time the ventrum of the penis is covered by scrotal skin flaps. The third possibility is to cover the penile shaft with free, thick, split skin grafts. The use of penile skin is preferable when possible since it provides a close-fitting but elastic covering for the organ. With scrotal skin this close fit is more difficult to obtain, especially around the base of the penis, and the appearance is generally less satisfactory. Free skin grafts have the disadvantages that they tend to contract and that they are inelastic and insensitive; they should be used only when other methods cannot.

It is now recognised that penile erection is not dependent upon compression of the crura by the ischio-cavernosus muscles against the bony rami, as was formerly supposed, but is due to an active increase in arterial inflow (Weiss, 1972). Separation of the crura from the bone should not, therefore, interfere with erection and in practice it does not (Fig. 2).

The above technique of penile lengthening has been employed by the author in 10 boys, adolescents and young men with epispadias, either alone or in association with bladder exstrophy. It has given satisfactory results both during primary reconstructions and also in the secondary correction of epispadiac deformities which had previously had inadequate surgical correction (Fig. 2).

The method has also been applied to one boy, aged 6 years, with micropenis associated with rudimentary testes and to another, aged 10 years, whose penile shaft sloughed following the misuse of diathermy during circumcision in infancy (Fig. 3). In these patients, because of the normal skeletal anatomy, an even greater lengthening of the penis was obtained than in the epispadiac cases.

Summary

Effective lengthening of a short penis, with maintenance of erectile activity, can be achieved by partial separation of the penile crura from the pubo-ischial rami.

The technique is applicable both to the congenital and the acquired short penis.

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Carcinoma of the Penis and Bleomycin Chemotherapy in Uganda

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In Uganda, carcinoma of the penis is the most frequently diagnosed malignant tumour in males, accounting for about 10% of all male cancers. Approximately 35 new cases of penile cancer are seen each year at Mulago Hospital, Kampala. Mulago Hospital is the teaching hospital for Makerere University Medical School. Calculations based on figures of the Kampala Cancer registry indicate the true incidence of carcinoma of the penis, in fact, to be less than that of liver cancer (Templeton and Bianchi, 1972) (Table I). Nevertheless the incidence makes a striking contrast with that of the United Kingdom where penile cancer accounts for less than 1% of male tumours, and a regional urology centre sees an average of 4 cases per year (Frew, Jefferies and Swinney, 1967).

Uganda has no radiotherapy facilities so that the only treatment of value available for carcinoma of the penis is surgical. Unfortunately a significant number of patients, 15% at Mulago Hospital (Kyalwazi, 1966), refuse surgery, and no doubt others, aware of the implications, prefer not to seek hospital treatment. Chemotherapy would be an attractive alternative to surgery but earlier trials have been disappointing (Kyalwazi, 1966).

A new antitumour agent, bleomycin, was discovered in Japan (Umezawa *et al.*, 1966). Early clinical trials (Ichikawa, Nakano and Hirokawa, 1969) indicated that bleomycin had some unusual properties including a particular affinity for squamous cell tumours and appeared to be effective in penile cancer.

There were compelling reasons for a clinical trial of such an agent in Uganda and experience with bleomycin has been acquired since 1970.

Bleomycin is an antibiotic, obtained from strains of *Streptomyces Verticillus*, which has an inhibitory effect on certain malignant cells. It is selectively concentrated in the skin and lungs and in certain tumours. Bleomycin, unlike most other antitumour agents, appears to have no significant haemopoietic or immunosuppressive effects (E.O.R.T.C., 1970).

Table I

Malignant Tumours in Uganda. Annual Figures for Males.

Tumours registered		Calculated frequency		Incidence per 100,000 population
Penis	111	Liver	381	7·9
Liver	110	Penis	208	4·3
Skin	104	Skin	196	4·1
Kaposi's sarcoma	78	Kaposi	146	3·0

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

Table II

Stage	Criteria	Number of Patients
I	Tumour confined to glans or prepuce	5
II	Tumour invading penile shaft or corpora	8
III	Tumour beyond stage I or II	2

Table III

Results of Bleomycin Therapy

<table>
<tr><th>Complete Regression</th><th colspan="2">Partial Regression</th><th>No Response</th></tr>
<tr><td>3</td><td colspan="2">11</td><td>1</td></tr>
<tr><td></td><td>Anticipated complete ("good")</td><td>Inadequate ("poor")</td><td></td></tr>
<tr><td></td><td>4</td><td>7</td><td></td></tr>
<tr><td colspan="2">Success</td><td colspan="2">Fail</td></tr>
<tr><td colspan="2">7</td><td colspan="2">8</td></tr>
</table>

Bleomycin has been widely evaluated in a variety of malignancies in various centres in Japan, Europe and USA. Published reports on its use in penile tumours are few. Ichikawa *et al.* (1969) had treated 8 patients of whom 2 showed complete, and 4 partial, tumour regression. Apart from an earlier report from Uganda (Kyalwazi and Bhana, 1973) other publications refer only to 1 or 2 cases of carcinoma of the penis (E.O.R.T.C., 1970; Jorgensen, Ohlsen and Andersen, 1971).

Patients and Procedures

Patients for bleomycin treatment were unselected. Those with penile cancer seen by one surgical firm at Mulago Hospital were offered chemotherapy. Some were unwilling to accept the rather prolonged stay in hospital which treatment entailed, and others defaulted. Histological confirmation of the diagnosis was obtained in all cases. A full clinical assessment was made, including chest radiology, haematological and bacteriological examinations, before starting treatment. If necessary a dorsal slit was made to visualise the tumour more fully. Tumours were staged according to criteria given in Table II. Stage III tumours were those which had extended beyond the situations of I and II—either by direct extension, lymph-node involvement or distant metastases. During treatment blood counts were done at least once weekly and chest X-rays at 2-weekly intervals.

Bleomycin was given intravenously, once or twice weekly, at a dose from between 30 and 60 mg. Treatment continued for as long as there was evidence of tumour response. When signs of toxicity occurred the drug was stopped for a period of 3 or 4 weeks and then restarted. The total dose of bleomycin given ranged from 180 mg to 1080 mg with a mean of 600 mg.

Table IV

Toxic Effects of Bleomycin
(9 of 15 patients)

Hyperpigmentation	7
Joint Pains	3
Alopecia	2
Anorexia	1
Fever	1
Sore-throat	1

Table V

Results of Bleomycin Therapy

Stage of Tumour	Result Cure	 Good	 Poor	No Response
I	2	3	0	0
II	1	1	6	0
III	0	0	1	1

The 15 patients reviewed in this report had ages ranging from 30 to 72 years with a mean of 49 years. At the time of presentation the duration of symptoms was between 2 months and 5 years with a median of 1 year. 5 patients had stage I tumours, 8 stage II and 2 stage III (Table II). Histological examination of the tumours showed one example of carcinoma *in situ*. The others all showed invasive squamous cell carcinoma of which 7 were described as well differentiated, 5 moderately well, and 1 poorly differentiated.

Results

(*a*) *Tumour Response* (Table III). Complete tumour regression occurred in 3 patients and partial regression in 11. Of those showing a partial response the tumour had almost completely regressed in 4 and complete regression was anticipated. In 7 the response was inadequate and it was necessary to complete treatment by amputation.

Only 1 patient showed no response at all. He died after having received 300 mg of bleomycin and at post-mortem examination widespread metastases were found in lymph nodes, liver, pericardium and adrenals.

(*b*) *Side effects*. There was no evidence of toxicity in 6 patients. The side effects occurring in the remaining 9 patients were of a relatively minor nature (Table IV). The most frequent side effect was hyperpigmentation of the face, finger nails and over bony prominences such as elbows and trochanters. It did not trouble patients and gradually disappeared when the drug was stopped. Hyperpigmentation was not considered a contraindication for starting a further course of treatment. There was no evidence of any haemopoietic effects, and pulmonary fibrosis, the one serious toxic effect which has been reported, was not seen.

Discussion

A useful, hopefully curative, response was obtained with bleomycin in 7 patients (47%). Once complete regression occurred no further courses of the drug have been given. The longest remission has been 2 years.

Table VI

Results of Bleomycin Therapy

Histology of tumour	Result			
	Cure	Good	Poor	No Response
In situ	1	0	0	0
Well differentiated	2	3	2	0
Moderately differentiated	0	1	3	1
Poorly differentiated	0	0	1	0

Table VII

Results of Bleomycin Therapy

Total Dose (in mg)	Result			
	Cure	Good	Poor	No Response
<250	0	1	0	0
250-500	2	1	1	1
501-750	1	2	2	0
751-1000	0	0	1	0
>1000	0	0	3	0

When the results are looked at further we can see a number of factors which appear to favour a successful outcome with chemotherapy.

(i) *Stage*. As might be expected the majority of successfully treated patients had Stage I lesions (Table V). The 1 patient with a Stage II lesion in the cure group had tumour extending onto the penile shaft but without apparently involving the corpora cavernosa. Conversely, all 6 patients with a poor response and Stage II lesions had clinical or histological evidence of tumours invading the corpora. It would seem that the involvement of the corpora, rather than the superficial extent of the tumour, is an important factor influencing the success of chemotherapy.

(ii) *Differentiation*. Table VI shows the results related to the histological classification of the tumour. The majority of good responses occurred in well-differentiated tumours. There have been other reports suggesting that the more highly differentiated tumours respond well (Jorgensen *et al.*, 1971).

(iii) *Dose*. Initially doses of 15-30 mg I.V. once or twice per week were given but the apparent lack of tumour response prompted increasing this to 45 or 60 mg which produced more encouraging responses. The total dose of bleomycin given was limited by the response achieved and the development of toxic effects. In some patients the course of treatment continued for up to 14 months. However, Table VII shows that all the good responses were achieved with total doses of less than 750 mg bleomycin. This suggests that there is little value continuing beyond a total dose of 750 mg in the hope of obtaining a cure, particularly

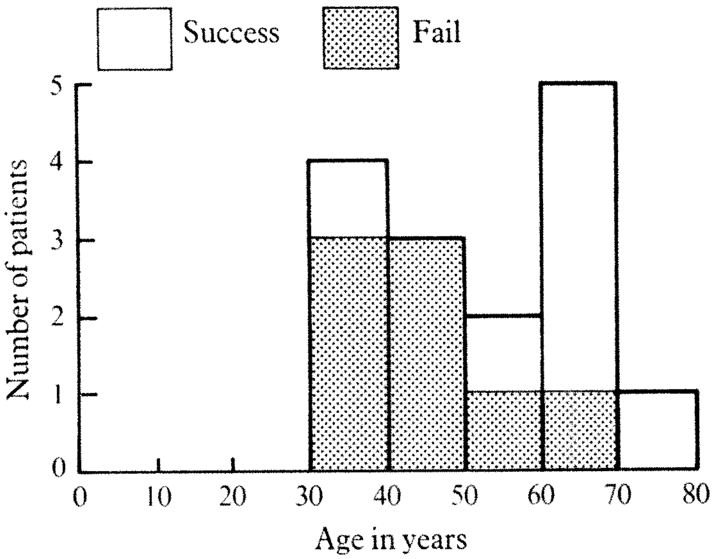

Fig. 1. Results of treatment related to age.

as pulmonary fibrosis, the only serious toxic effect of bleomycin, is said to be more likely with higher doses.

Although in this series no patient showed clinical or radiological evidence of pulmonary toxic effects one patient who had achieved complete tumour regression with a total dose of 540 mg is known to have died at home after developing a cough 3 months after treatment. It was not possible to obtain a post-mortem examination so no conclusions can be drawn as to whether he had developed a fatal pneumonia superimposed on drug-induced pulmonary fibrosis.

(iv) *Age*. The mean age of patients with cancer of the penis in Uganda is around 50 years (Kyalwazi, 1966) which is approximately 10 years less than that for UK and USA (Frew *et al*., 1967; De Kernion *et al*., 1973). In this series 3 patients were aged 30 years. However Figure 1 shows that only 1 of the successfully treated patients was under 50 years. The tumours of the younger patients of this series show a tendency to be more advanced and less differentiated (Figs. 2 and 3). This is a disappointing finding as it is the younger patient, in particular, who is most likely to decline amputation and for whom one would wish to offer a non-operative alternative treatment.

The Place of Bleomycin Therapy

There is no doubt that bleomycin is more effective than previously available drugs in the treatment of squamous cell carcinoma of the penis. However the response is least satisfactory in the very situations where surgery is most likely to be refused by the patient. It may be possible to increase the efficacy of chemotherapy by combining bleomycin with other agents particularly as it appears to have a different mode of action from other oncolytic drugs (Suzuki, Nagai and Yamaki, 1969). A combination of 2 or 3 drugs is at present being tried in Uganda (Kyalwazi, 1973).

Bleomycin has other limitations. The prolonged nature of the treatment, usually necessitating hospital admission is a disadvantage, particularly in a country like Uganda where hospital facilities are grossly overburdened. In view of the relatively few toxic effects treatment could be

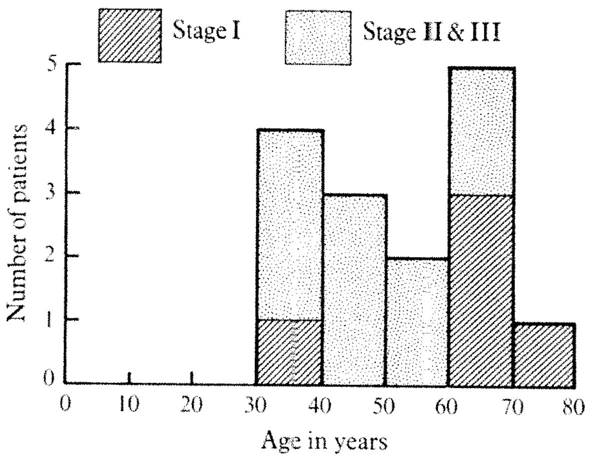

Fig. 2. Age and tumour stage.

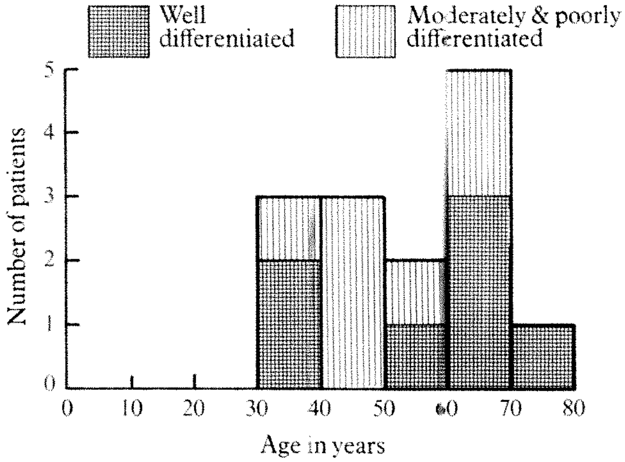

Fig. 3. Age and tumour histology.

given on an out-patient basis, but it is necessary to watch the patient carefully for signs of pulmonary complications both during treatment and for a few weeks after.

For well-differentiated tumours confined to the glans or penile skin bleomycin can be recommended. If, after a total dose of 750 mg the tumour response is inadequate treatment should be completed by amputation. Other tumours are best treated surgically, reserving bleomycin for patients who cannot be persuaded to accept amputation.

In countries where radiotherapy facilities are available bleomycin may provide a useful alternative treatment for Stage I tumours but it probably does not offer any significant advantage over radiotherapy. The majority of tumours will continue to be dealt with surgically.

Bleomycin may well be useful for the palliation of inoperable tumours. In London, we have recently treated a 54-year-old patient who developed skin metastases following penile amputation and bilateral inguinal node dissections. After 300 mg of bleomycin the lesions had shown partial regression and pain and oedema decreased in a most encouraging way.

In Uganda where penile cancer is so common there is considerable scope for preventive measures. As in other countries carcinoma of the penis is extremely rare in the circumcised (Kyalwazi, 1966). It has been suggested that infantile circumcision should be pursued as a public health policy (Dodge and Linsell, 1963). Many objections to this approach can be raised and it seems likely that an improvement in the standards of personal hygiene can be equally effective. There is some evidence that the incidence of carcinoma of the penis has already declined. Nevertheless where ritual circumcision is performed for religious reasons, as amongst Moslems, or as an initiation rite as in the Masaba tribe, its practice should not be discouraged.

Conclusions

Carcinoma of the penis will usually regress in response to bleomycin therapy.

Bleomycin is more effective in penile cancer than previously available drugs.

Factors which favour a successful response to bleomycin are: tumour confined to the glans, prepuce or penile skin; a high degree of tumour differentiation; age over 50 years.

Complete tumour regression will usually be achieved by a total dose of less than 750 mg bleomycin. Larger doses may induce further regression, which could be useful surgically, but a curative response is unlikely.

Bleomycin may be useful for the palliation of inoperable tumours or metastases.

Serious toxic effects of bleomycin are uncommon.

Summary

Bleomycin chemotherapy in the treatment of carcinoma of the penis has been evaluated in 15 patients in Uganda. Tumour regression occurred in all but one patient. Complete regression was obtained in 7 patients (47%), none of whom received more than 700 mg of the drug. In the remaining patients the response was incomplete and amputation was performed.

Well-differentiated tumours confined to the glans or penile skin in older patients appear most likely to respond successfully.

Side effects of a relatively trivial nature were observed in over half the patients, but pulmonary fibrosis was not encountered.

The bleomycin study was supported by the Cancer Research Campaign (formerly the British Empire Cancer Campaign).

The tables were prepared by the Department of Medical Illustration, the Institute of Urology, London.

Mr J. C. Park, Consultant Urologist, Greenwich District Hospital kindly gave permission to refer to one of his patients.

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Book Reviews

Current Concepts in the Management of Gram-Negative Bacterial Infections. Edited by ALLAN R. RONALD. International Congress Series No. 318. Amsterdam: Excerpta Medica, 1974. £12·00

This publication consists of a series of papers presented at a Symposium in Montreal on April 10th 1973 on gram-negative bacterial infections and their management. The topics discussed represent a comprehensive review of such infections in paediatrics, surgery and the respiratory tract and include the phenomenon of bacteraemic shock. The urologist will be especially interested in the final two papers which deal with the laboratory, clinical and radiological diagnosis of infections of the urinary tract and their subsequent management, and a consideration of the clinical pharmacology of gentamicin and kanamycin in normal patients and in those with impaired renal function.

The efficacy of haemodialysis and peritoneal dialysis in the removal of these aminoglycosides from the blood is considered. In patients with normal renal function ototoxicity is most likely to occur in patients with peak concentrations in excess of 10 μg/ml. In those with impaired renal function where the half life of gentamicin is markedly prolonged, it is suggested that ototoxicity is more closely related to the product of time and plasma concentrations rather than the peak level. A case history illustrating this point is presented. Formulae for calculating the appropriate dosage of gentamicin and kanamycin in patients with renal failure are suggested.

(*Note:* On page 15 in a description of the factors essential for the growth of *Haemophilus influenzae* X factor is described as nicotinamide adenine dinucleotide and V factor as haemin; in fact the converse is true).

H. R. I.

A Handbook of Urinalysis and Urinary Sediment. By N. A. KURTZMAN and P. W. ROGERS. Pp. ii + 103. Springfield, Illinois: Charles C. Thomas. 1974. £4·25.

Urine microscopy was, for many years, the most neglected investigation in medicine. At the moment it is enjoying a modest revival. It has finally dawned on the profession that if you throw away your antiquated monocular microscope with a rich flora of bacteria, casts and crystals in its sadly abused lenses, buy a good binocular and treat it with loving, tender care, you can garner a rich harvest of diagnostic material and enjoy a new aesthetic pleasure.

This short manual first describes chemical analysis of the urine. This section includes a number of tests which have now been superseded by the much simpler dipsticks, but there is also a good deal of valuable information on less common analyses with full details of how to prepare the reagents.

The most useful section, in my view, is the part describing the urinary deposit, with excellent colour illustrations. These are reproduced at a magnification of 1,000 with good definition, considering the difficulty of focusing at high magnification on thick objects like casts. I was able to identify all but one of the illustrated urinary findings without reading the sub-titles, which is a high tribute to the standard of photography. This section perpetuates the myth that granular casts are degenerate cellular casts, but in most other respects the information is up-to-date, concise and useful. There is a final section describing the urinary abnormalities in different renal diseases.

If you have any money left over after buying that new microscope, get a copy of Kurtzman and Rogers to put beside it!

D. N. S. K.

Needle Biopsy. By T. J. DEELEY. Pp. viii + 170 with 33 illustrations. London: Butterworth. 1974. £3·50.

This small book describes needles and biopsies and needle biopsy in painstaking detail and with commendable clarity. Dr Deeley is an advocate of the high-speed drill biopsy method, basing his enthusiasm upon 25 years' experience. The oft quoted criticisms that the method yields inadequate and inaccurate information, risks tumour spread and may be potentially hazardous, are considered responsibly. Fears are allayed by facts. Oncologists may choose to read only sections 17 and 20. How often do we feel a nodule and guess? How much better to needle it and know.

R. R. H.

Books Received

Functional Anatomy of the Urogenital System. By D. BULMER. London: Pitman Medical. 1974. £1·90.

ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

La Nouvelle Presse Médicale

By John Grieve

"Unusual Manifestations of Henoch-Schönlein Purpura—Localisation in the Testis and Neurological Disturbances." B. Labrune and B. Vignes. (1974, **3**, 1023-1025.)—This paper from Paris reports unusual clinical features in 2 cases of Henoch-Schönlein purpura. Testicular localisation is rare, should not be confused with torsion, and should be treated with corticosteroids. The neurological disturbances vary, occur more often (than is admitted) and may pass unnoticed. The less severe forms present as confusion or altered behaviour and should be recognised by electro-encephalography.

"Primary Hyperparathyroidism." C. Dubost and D. Maury. (1974, **3**, 359-364.)—In this study from Paris 123 patients were diagnosed as having primary hyperparathyroidism. All were explored surgically and the diagnosis confirmed in 100 cases. Among the latter were 87 simple adenomas, 7 double adenomas, 3 hyperplasias and 3 cancers. The negative explorations tended to occur in the "mild" cases and here diagnostic difficulties are greatest. For some months the authors have been able to do blood parathormone levels and they believe that these estimations are of considerable diagnostic help in the so called "mild" forms.

"Retroperitoneal Fibrosis—a Case complicated by Involvement of the Femoral Artery and Tricuspid Insufficiency." A. Barrillon, P. Thiroloix, J. Baragan, J. Felix and A. Gerbaux. (1974, **3**, 337-379.)—These authors report the case of a 48-year-old woman who had quite severe bilateral claudication. Investigation showed that she had retroperitoneal fibrosis with in addition arteriopathy involving both superficial femoral arteries, and the tricuspid valve. The retroperitoneal fibrosis caused lateral displacement of the left kidney and ureter and there was no function on the right. The patient had taken 6·6 mg methysergide daily for over 5 years. When the dose was reduced the claudication and backache improved, but prednisolone over a period of 7 months produced little change in function. The authors claim that this is the first example of retroperitoneal fibrosis involving the tricuspid valve.

Der Urologe

By John Grieve

"Fibrous Polyps of the Ureter." J. E. Altwein, H. D. Walff and K. Stockamp. (1974, **13**, 86-89)—In contrast to papillary tumours ureteric polyps are rare benign tumours. They may present in childhood and adolescence with colicky pain and haematuria. X-ray investigation may arouse suspicion as to the diagnosis. The authors report 2 cases, one a 14-year-old girl and the other a 7-year-old boy in whom the diagnosis was confirmed by frozen section and conservative surgery with restoration of the continuity of the ureter was the treatment.

"In-vitro Experiments on the Effects of Exogenous Progesterone on the Motility of the Human Ureter." H. Anger. (1974, **13**, 35-36.)—Motility studies were done in Kiel on the isolated human ureter segment. The addition of progesterone to Tyrode solution containing a segment of ureter inhibits electrically induced contraction of that ureter. This decrease in motility is characteristic of pregnancy and appears early. The author suggests that these experiments support the hypothesis of a hormonal aetiology for ureteral atony in pregnancy.

"The Antibacterial Effect of Prostatic Secretions." J. Kohliček, T. Stáňková, J. Rydlinková, S. Kočvana and M. Hatala. (1974, **13**, 31-34.)—In this paper from Czechoslovakia the antibacterial effect of prostatic secretion was examined in 139 patients. Gram-positive organisms were well-controlled, but there was no effect on gram-negative ones. The effect is bacteriostatic and is greater in young than older people. It is also independent of the number of leucocytes present.

"Bleomycin for Malignant Tumours of the Male Genital Tract." P. Rathert, B. Terhorst and W. Latzeyer. (1974, **13**, 67-71.)—This is essentially a preliminary but interesting report. Squamous cell carcinoma of the penis and germinal testicular tumours were treated with bleomycin alone or in combination with surgery, radiation and/or cytostatic drugs. Early carcinoma of the penis did well with local excision and in younger patients combined radiation and Bleomycin were effective in teratocarcinoma and chorio-epithelioma of the testis. Trials of a combination of bleomycin, actinomycin D and Vinblastine have been encouraging.

"630 Biopsies from Urinary Bladder Tumours—an Analysis of the Pathological Anatomy with Special Emphasis on the Potential Malignancy of Papillomas." U. Bettendorf. (1974, **13**, 56-58.)—This series from Frankfurt shows 4 times as many bladder tumours in men as in women. The average age of the patients was between 63·7 and 68 years depending on the type of tumour. About half of the malignant tumours began as apparently benign papillomata. Where a papilloma recurs over 41% of these develop frank malignancy and these malignant tumours quite frequently become undifferentiated. The author emphasises the importance of prolonged and careful follow-up.

Deutsche Medizinische Wochenschrift

By John Grieve

"Primary Hyperparathyroidism with Mediastinal Adenomas." F. Kumnerle, M. Rothmund, L.

DIETHELM and H. BRUNNER. (1974, **99**, 983-988.)—Between 1965 and 1973 42 parathyroid tumours were removed from 38 patients. In 7 the adenoma was in the mediastinum and 5 of these were found in the anterior mediastinum after exploration of the neck. Two were in the posterior mediastinum, one being found during a second operation and the other during a third. (Approach right sided thoracotomy.) The authors have used radio-immunological assay of parathormone in local venous blood and found this the most promising pre-operative aid to localisation.

"Spontaneous Rupture of the Kidney as a Complication of Anticoagulant Therapy." L. WEISSBACH, P. BRUHL, B. HUNERMANN, H. SCHNEIDER, and W. KOZUSCHEK. (1974, **99**, 1135-1137.)—In 2 patients on anticoagulant therapy spontaneous rupture of the kidney was seen following massive parenchymal haemorrhage in the kidney. One patient had renal arteriosclerosis and the other interstitial nephritis and this existing disease contributed to the problems of anticoagulation. The advantages and risks require careful consideration in all anticoagulant therapy.

"Familial Primary Hyperparathyroidism." M. EISEN, K. BUSSE, J. BEYER, V. GRABS, J. HAPP and R. SCHAFER. (1974, **99**, 1128-1134.)—Three siblings showed primary hyperparathyroidism and their father had died in uraemia with a chronic stone history. Each sibling had a recurrence of the adenoma after removal. In this family there were no other obvious endocrine upsets to suggest multiple endocrine adenomatosis. All adenomas must be removed and the affected family require careful screening from the urological and endocrine angles.

"The XXYY Variant of Klinefelter's Syndrome." O. P. HORNSTEIN, H. D. ROTT, G. SCHWANITZ and G. GROSSE. (1974, **99**, 248-251.)—On clinical examination and testicular biopsy a 26-year-old patient had a typical Klinefelter's syndrome. In addition, however, he showed gigantism (height 2·06 metres), various skeletal anomalies and deformities, diminished intelligence and some psychic abnormalities. The genetic karyogram was 48XXYY. The authors attempt to differentiate the 48XXYY from the more common 47XXY on clinical grounds.

Surgery, Gynecology and Obstetrics

By THOMAS MOORE

"What's New in Surgery: 'Urology'."—JAMES F. GLENN. (1974, **138**, 222-224.) This annual review, part of "What's New in Surgery" of the 15th Clinical Congress of the American College of Surgeons, included among others, reference to the following:—ribonucleic acid tumour viruses in urothelial tumours, radiation of malignant renal and prostatic lesions, advances in chemotherapy of Wilms' tumours and testicular tumours, reconstructive operations in the urinary tract, renal transplantation, calculus disease, urinary tract infections, medical treatment of both benign and malignant prostatic disease, chromosome abnormalities in congenital lesions of the urinary tract, tissue culture in the study of malignant disease, ultrasonography, 6-hydroxydopamine adrenergic nerve destruction in animals and a study of its effects on urodynamics, the intestinal transport of oxalate and its relation to oxalate urinary stones, development and function of the human testis. A full bibliography is always available to those attending the Congress.

"Renal Tissue Oxygen Tension during the Early Phase of Canine Endotoxin Shock." MALTE M. LINDER, WILHELM HARTEL, PETER ALKEN and ROMAN MUSCHAWECK. (1974, **138**, 171-173.)—The authors working in West Germany have studied in dogs, during endotoxic shock following the injection of a standard dose of ground *E. coli* suspension, arterial and venous blood pressures, blood flow in left renal artery and the renal surface pO2. They have shown that the tissue pO2 falls rapidly but recovers to 90% of normal within 60 minutes in spite of a continued reduction of renal arterial flow to 41% of normal. These results contrast with their findings in haemorrhagic shock, in which tissue pO2 is directly related, after re-infusing, to renal arterial flow.

"Radiocholesterol Adrenal Images for the Localization of Pheochromocytoma". MARTIN F. STURMAN, DAVID C. MOSES, WILLIAM H. BEIRWALTES, TIMOTHY S. HARRISON, RODNEY D. ICE and RICHARD P. DORR. (1974, **138**, 177-180.)—The technique of using ^{131}I-19 idiocholesterol adrenal gland imaging and percentage uptake test by these authors has been used in 6 patients with a known unilateral pheochromocytoma. Although the radioactive substance does not localise in the pheochromocytoma itself, by the absence of decreased tracer activity in the images the affected adrenal was correctly identified preoperatively in all 6 patients. They believe the technique is a valuable help in the localisation of medullary adrenal tumours and is particularly useful in patients who cannot tolerate, or who have had unsuccessful angiography.

"Evaluation of Corticosteroid Therapy for Acute Renal Allograft Rejection." GORDON C. VINEYARD, STEPHEN Z. FADEM, JAN DMOCHOWSKI, CHARLES B. CARPENTER and RICHARD E. WILSON. (1974, **138**, 225-229.)—From the Peter Bent Brigham Hospital, Boston, the authors report their results of a retrospective study of 110 consecutive renal allograft recipients and compare the results of two separate programmes of steroid treatment. Full details of the 2 programmes are given and no difference in their effectiveness was demonstrated.

"Machine Preservation of 302 Human Cadaveric Kidneys for Transplantation." THOMAS C. MOORE, THOMAS S. ENGLISH and THOMAS V. BERNE. (1974, **138**, 239-243.)—The details of the organisation and results of the Greater Los Angeles Mobile Kidney Preservation Unit are presented. By pulsatile perfusion with cryoprecipitated plasma during the last 24 months the authors have preserved 302 kidneys from 1[illegible]2 cadavers; 48 kidneys were not transplanted because of poor perfusion. Donor ages range from 1½ years to 65 years with the majority in the 10-30 years range. Donor deaths were mainly from blunt and penetrating head trauma or spontaneous intercranial haemorrhage. Perfusion time varied from 3-70 hours and averages 21·9 hours. Early post-transplant function varying from immediate and continuing good function, immediate good function with accelerated rejection, slow initial function and non-function. From their studies the authors believe that pre-existing antibodies largely the result of prolonged dialysis were mainly responsible for early post-transplant malfunction. Their experience suggests that more than 90% of kidneys which perfuse well on the Belzer machine should function well after transplantation and those that do not are likely to be due to recipient pre-sensitisation to donor transplant antigens, which appears to increase with long periods of haemodialysis. They suggest that renal transplantation should be performed prior to, or only shortly after, the initiation of haemodialysis.

The Australian and New Zealand Journal of Surgery

By J. P. Maddern

"Vesico-Ureteric Reflux after Renal Transplantation." D. Urquhart-Hay, J. McIlwaine and C. B. S. Stephenson. (1973, **43**, 225-228.)—The authors report from the Wellington Hospital, New Zealand, their experience with a tunnel and cuff method of implanting the ureter in renal homotransplantation. They have used the Williams and Eckstein modification of Paquin's method of reimplantation, where the ureter is passed through an oblique muscular and submucosal tunnel in the bladder wall with the creation of a nipple on its end which is anchored in turn to the bladder wall. This method has been used in 49 patients receiving cadaveric homografts, 20 of whom have been investigated radiologically for evidence of vesico-ureteric reflux and stricture formation. These 20 patients have been submitted to micturating cystourethrography between 4 and 42 months after transplantation and vesico-ureteric reflux occurred in 1 case. Intravenous pyelography revealed no evidence of renal backpressure, but there was some slight fullness of the ureter in 1 case and a small diverticulum noted adjacent to the site of implantation on another occasion.

"Colocystoplasty: Bladder Replacement after Total Cystectomy." Peter T. Bruce. (1973, **43**, 270-273.)—The author reports from the Royal Melbourne Hospital and Sandringham and District Memorial Hospital in Victoria his experience in colocystoplasty as a method of bladder replacement after total cystectomy for carcinoma of the bladder in 10 patients. The ages ranged from 45 to 72 years. In the 1 female case the carcinoma involved the anterior vaginal wall, which necessitated an anterior exenteration. In 2 there were multiple papillomata, which were uncontrollable by endoscopic means, and in these a total cystoprostato-seminal vesiculectomy was carried out. The remaining 8 patients had solid transitional cell carcinomata of at least a Stage T_2M_{III} U.I.C.C. classification. These patients in addition had a pelvic lymph adenectomy, but no urethrectomy. The technique was similar to that described by G. V. Ong (1970), the ureters being anastomosed using the Leadbetter techniques. Although the postoperative course carried a formidable morbidity there were no operative deaths. 8 of the patients were alive for periods varying from 5 years to 1 year and 3 months. There were 2 deaths, one at 8 weeks, another at 22 months, both dying from metastases. Only 1 patient was totally continent both by day and night, the remaining patients experienced difficulties with continence at night and 1 patient was incontinent by both day and night. A low serum potassium level was noted in 6 patients, only 1 however required an oral supplement. All patients passed mucus in varying quantities without apparent difficulty. Frequency was not an undue problem, but 50% of the group showed reflux, 2 of whom experienced chronic or recurrent urinary tract infections. Two patients developed fistulae, one a vesico-vaginal fistula and one a vesico-rectal fistula.

"Post Prostatectomy Bleeding: Active Management by Early Endoscopic Haemostasis and Packing in a Series of 3,219 Prostatectomies." Robert D. Wines, Victor Lane and J. Dermot O'Flynn. (1973, **43**, 274-277.)—The authors review the results of active early management of post-prostatectomy bleeding in a series of 3,219 patients treated in the Urological Department of the Meath Hospital, Dublin, and the Department of Surgery, Trinity College, Dublin. 136 patients with heavy bleeding or clot retention after prostatectomy were returned to the operating theatre for 162 procedures. Early endoscopic evacuation of blood clot and subsequent haemostasis with the use of a resectoscope produced satisfactory control in 124 of the 136 patients. 26 patients had the prostatic fossa packed either at the time of prostatectomy or after failed endoscopic haemostasis. Packing of the prostatic fossa was associated with a sizable morbidity. The problems encountered including bleeding following removal of a pack, temporary suprapubic leakage, a suprapubic fistula and wound infection, burst wound, epididymitis and incontinence. An over-all mortality of 1·6% was reported, there were no deaths reported from those who had a prostatic fossa pack as an initial procedure, although 7 deaths occurred after endoscopic evacuation alone and one after endoscopic evacuation and later packing of the prostatic fossa.

"The Treatment of Benign Prostatomegaly by Injection." Hussein Bin Mohamed Salleh. (1973, **43**, 278-280.)—The author reports from the General Hospital, Johore Bahru, Malaysia, the results of the treatment of 32 cases of benign prostatomegaly by perineal injection of a sclerosant fluid. The 32 patients presented with varying symptoms of prostatomegaly, 5 had complete retention. The diagnosis was confirmed with a transrectal prostatic biopsy using a Vim-Silvermann needle. Following injection of 3 ml of a mixture of carbolic acid, glacial acid, glycerin and distilled water using a local anaesthesia 25 of the 32 patients experienced pain and tenderness in the perineum in the first 24 hours which was controlled by oral analgesics. Most patients experienced beneficial effects within 2 days of the injection, although 4 patients required a second injection before improvement was noted. Using relief of symptoms and an assessment of residual urine, complete success was claimed in 27, moderate success in 3 and a failure of treatment in 2 of the 32 patients. There was 1 case of prostatic abscess reported which settled with intensive antibiotic therapy. A follow-up of between 6 and 7 years revealed no recurrence in 30 of the 32 patients. The two in whom no success was reported underwent transvesical prostatectomy, when no undue difficulty was experienced in enucleating the enlarged prostate at operation. Blood loss on each occasion was less than 200 ml.

"Spontaneous Intraperitoneal Rupture of Pyonephrosis." V. R. Minocha, M. L. Mehrotra and N. N. Khanna. (1973, **43**, 281-282.)—These authors from the Banaras Hindu University, Varanasi, India, report a case of intraperitoneal rupture of a pyonephrosis. This report supplements 11 previously reported cases. A 34-year-old woman was under investigation for a right loin mass when she developed quite acute symptoms of peritonitis and responded very poorly to treatment and died some 14 hours after the onset of abdominal pain. The subsequent autopsy revealed an intraperitoneal rupture of a pyonephrosis. The diagnois was complicated by the fact that amoebic liver abscess is endemic in that region of India.

"Choriocarcinoma of the Testis: Case Report with Review of the Literature." N. V. Raghavaiah and B. S. Rao. (1973, **43**, 283-285.)—The authors report from the King George Hospital, Visakhapatnam, a case of choriocarcinoma of the testis. This patient presented with a 6-month history of a swelling in the left scrotum and haemoptysis. Investigations confirmed the presence of an enlarged left testis with an irregular surface of variable consistency. The patient exhibited bilateral gynaecomastia of 3 months' duration. The chorionic gonadotrophins were elevated and an Ascheim-Zondek test was positive with 1/1,000 dilution of the urine. Chest X-ray showed bilateral multiple secondary deposits. An orchidectomy was performed, but the patient died despite use of oral Methotrexate 35 days later.

"The Ureter in Renal Transplantation: Results of a Simple Technique of Uretero-Vesical Anastomosis." G. J. A. Clunie, K. J. Siddle, L. C. J. Hartley and I. R. Hardie. (1974, **44**, 12-16.)—The authors report from the Department of Surgery, University of Queensland the urological complications which have arisen in a consecutive series of 50 renal allotransplants in which a simple uretero-vesical anastomosis was carried out. Operations were performed in a 3½-year period between September 1969 and February 1973 and a minimum of 6 months' follow-up was carried out on all patients. Ureterovesical anastomosis was carried out through a 3-cm incision in the bladder wall, the ureter being anastomosed to bladder mucosa by means of a continuous 4/0 cat-gut suture. The bladder muscle was loosely closed over the ureter forming a short tunnel. The extra-vesical drainage was by means of Redivac closed suction. A closed system of continuous catheter drainage was maintained for 3 days, after which the catheter was removed and the drain was removed some 24 hours later.

Infusion intravenous pyelography was carried out at intervals of from 7 to 21 days following the transplantation. These pyelograms demonstrated 3 cases of minor degree of obstruction at the uretero-vesical junction, one of whom required excision of a lymph cyst to relieve obstruction. There were 4 cases of urinary leakage. One minor leak responded to reinsertion of a urethral catheter and continuous drainage. In the other 3, exploration was required. One patient had a sloughing of the distal 3 cm of the ureter requiring secondary reimplantation, another patient had sloughing of the whole length of the transplanted ureter whilst in a third a small suture line leak was treated by local over-sewing and reinsertion of catheter drainage.

5 cases showed evidence of reflux into the transplanted ureter, but post-operative urinary infection which occurred in 10 cases in the whole series was not encountered in this group.

The authors consider the incidence of urological complications with this simple method of uretero-vesical anastomosis compares well with other reports.

"Priapism: An Unusual Sequel of Appendicectomy: Case Report with Review of the Literature." S. Gue. (1974, **44**, 60-62)—The author describes a case of a 17-year-old male aborigine who was admitted to the Broken Hill Hospital in New South Wales with the classical signs of an acute appendicitis. Some 36 hours after appendicectomy he complained of a painful erection which did not resolve with conservative measures. Some 72 hours later he had a corpus-saphenous bypass performed on the right side with an immediate relief of the priapism. Some 12 hours following operation there was still considerable oedema of the penis, but the pain and the erection had ceased. He developed a local haematoma, however, which required evacuation, following which his heparin administration was discontinued. The oedema settled slowly, but he was discharged from hospital on the 12th post-operative day and some 6 weeks later at follow-up in the Out-Patient Department he reported normal sexual activity.

Annales Chirurgiae et Gynaecologiae Fenniae

By J. V. Mandel

"Control of Infection after Prostatectomy." P. Nummi, J. Soini and J. Permi. (1973, **62**, 142-145.)—The incidence of urinary infections and epididymitis in 226 patients whose prostates were enucleated transvesically, is presented. On admission, 25% of them had a urinary infection, according to their histories, 3% contracted transient infections, in the course of bladder drainage or operation. Follow-up examinations revealed that the infection persisted in only 8% Closed drainage was applied by indwelling catheters, and prophylactic chemotherapy was given with preoperative bladder drainage, and after operation. No vasectomy was performed, and the incidence of epididymitis was 1%.

"Vaginal Metastasis from Transitional Cell Carcinoma of the Left Kidney Pelvis." K. Kawabe and T. Kawamura. (1973, **62**, 169-171.)—The rare occurrence of vaginal secondary to a transitional cell carcinoma of the left kidney pelvis is presented. In the opinion of the authors only one case has been described in the literature, so far.

Rozhledy V Chirurgii

By J. V. Mandel

"A New Uretero-neo-cystotomy in Kidney Transplantation." J. Hejnal, M. Hahn, P. Málek, M. Kestlerová and R. Metyš. (1974, **53**, 272-275.)—The authors describe a new method of antireflux uretero-neo-cystotomy. It has been used in 20 kidney transplants, urinary fistula occurred only once, and vesico-ureteric reflux in 3 out of 14 patients where cystograms were taken. The results indicate that this method is an improvement on the previous ones. It prevents vesico-ureteric reflux, and avoids the greatest risk, *i.e.* urinary fistula.

"A Contribution to Radical Treatment of Tumours of the Urinary Bladder and Solitary Tumours of the Lungs." V. Šimon, F. Řehák and V. Prošek. (1974, **53**, 2: 101-103.)—The history of two patients suffering from carcinoma of the bladder and the lungs is described. In one patient a tumour of the lung developed 8 years after prostato-vesiculo-cystectomy for carcinoma, the other suffered from a solitary secondary of the lung.

Journal de Chirurgie

By John Grieve

"The Reliability of Ultrasonic Investigation in Renal Disease." F. Weill, D. Gallinet, J. R. Krachenbuhl and M. Bittard. (1974, **107**, 139-150.)—These workers in Besançon review the results of urography and ultrasonic tomography in 144 patients with renal disease. The error was only 3% and most errors occurred in the early cases when the ultrasonic apparatus was less efficient and the authors less experienced. No error was made in classing a malignant tumour as benign. It was possible to decide the appropriate operation on the basis of urography and the ultrasonic results thus reducing the necessity for renal arteriography.

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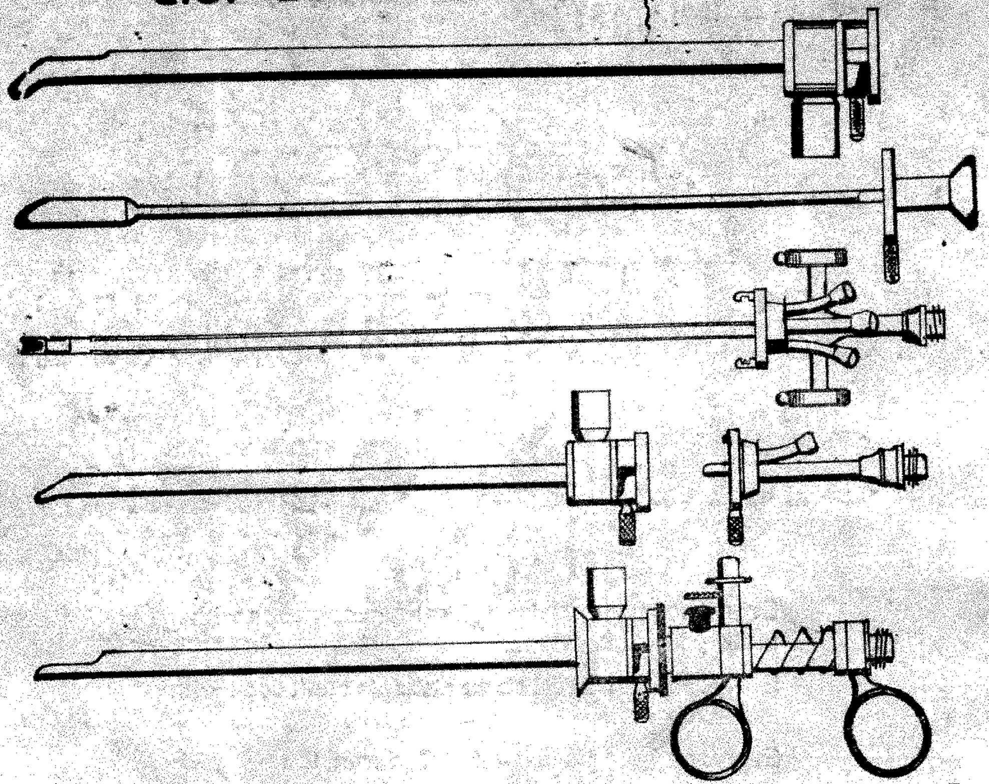

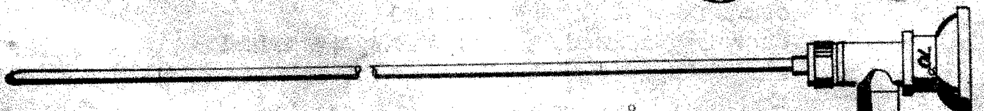

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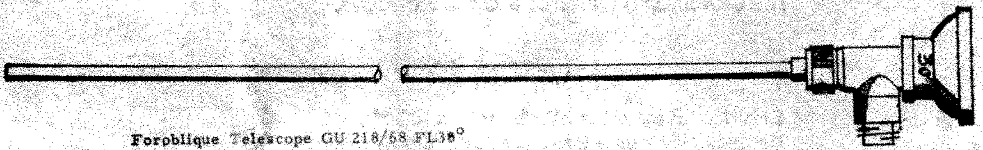

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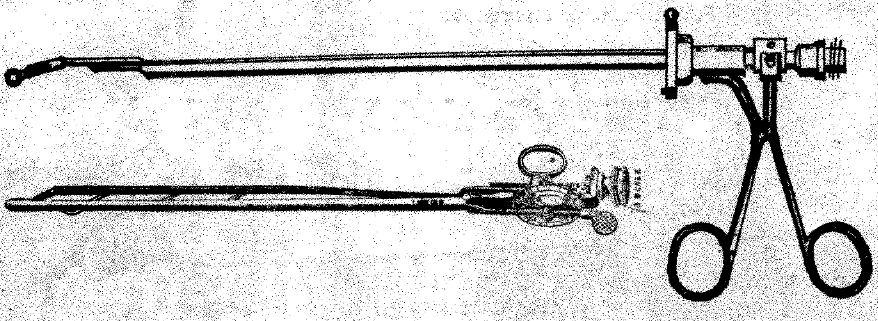

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